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Selective inhibition of HDAC6 affects ciliogenesis and prevents glioblastoma growth

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Introduction: Histone deacetylases (HDACs) are critical regulators of gene expression and have been exploited in the treatment of cancers; however, pan-HDAC inhibitors can lead to off-target effects and toxicity. HDAC6-selective inhibitors have recently garnered interest as they alter the acetylation of non-histone regulatory proteins implicated in tumor-related processes. One critical function of HDAC6 is to regulate cell cycle progression by triggering the retraction of cells' primary cilium before entering mitosis. We previously reported that cilia are routinely detected in GBM biopsies and that the majority of GBM patient-derived cells can give rise to ciliated progeny. Our preliminary data suggest that cilia persist in all phases of the cell cycle except mitosis. Since recent reports suggest HDAC6 is often overexpressed in GBM biopsies, we hypothesized that inhibiting HDAC6 will slow GBM growth by disrupting ciliogenesis.

Objective: To determine the relationship between HDAC6, primary cilia, and GBM cell proliferation.

Methods: We treated patient GBM-derived cells with vehicle or ACY-1215, a selective HDAC6 inhibitor, and measured cell viability, cell cycle phase distribution, ciliogenesis, and proliferative abilities of GBM cell lines with or without KIF3A (an essential regulator of ciliogenesis).

Results: HDAC6 was expressed in both patient cell lines that we examined. ACY-1215 treatment significantly reduced GBM cell proliferation, increased the number of cells in the G2/M phases, decreased cell viability in a dose-dependent manner (IC_{50} ~500nM), and increased apoptotic cell death. Surprisingly, ACY-1215 exposure significantly decreased or increased the percentage of ciliated GBM cells, depending on the cell line and time point analyzed post treatment. Notably, ACY-1215 did not affect the viability of GBM cells that lack cilia following the knockout of KIF3A. CONCLUSION: Selective HDAC6 inhibition slows GBM growth by affecting cell cycle progression and cell survival in a KIF3A/cilia-dependent manner. Future studies will focus on elucidating the molecular mechanisms underlying these effects.

Biography

Lan Hoang-Minh completed her doctoral studies in the Department of Biomedical Engineering at the University of Florida in Gainesville, Florida, USA. She is now a postdoctoral fellow in the laboratory of Dr. Matthew Sarkisian, studying the molecular and cellular mechanisms governing the proliferation of glioblastoma cells. Particularly, her postdoctoral work has focused on examining the role and characteristics of primary cilia, small cellular organelles recently frequently observed in human patients' glioblastoma biopsies and derived cell lines. In collaboration with a strong team of brain tumor investigators at the University of Florida, she has been investigating how these organelles and associated proteins may be involved in tumor pathogenesis and possibly resistance to standard-of-care therapy. She has also been collaborating with Dr. Loic Deleyrolle in examining the metabolic characteristics of fast and slow-cycling glioblastoma cells and various metabolic strategies to target those cell populations. She recently received a two-year American Brain Tumor Association Basic Research Fellowship Grant.

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