Lan B. Hoang-Minh et al., J Neurol Neurophysiol 2017, 8:4(Suppl)
DOI: 10.4172/2155-9562-C1-052

Key roles of mitochondrial function and lipid metabolism in slow-cycling glioblastoma cells

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Malignancies often exhibit rewired metabolism in order to satisfy the major energy and biosynthesis requirements of rapidly growing tumors. Despite the presence of sufficient oxygen in their environment, tumors frequently exhibit elevated glycolysis. This metabolic reprogramming to glycolysis, known as the Warburg phenomenon, has commonly been associated with an impairment of mitochondrial function, thus restricting the metabolism of alternative substrates and limiting tumor cells' metabolic diversity and adaptation. Here, we demonstrate that glioblastoma (GBM) tumor cells display metabolic heterogeneity, with fast-cycling cells harnessing anaerobic glycolysis and slow- cycling cells oxidative metabolism to support their growth and survival. We report the existence of SCCs in GBM, cells that display migration, invasion, and chemoresistance characteristics that might underlie tumor recurrence. SCCs consistently demonstrate heightened mitochondrial respiration activity as well as increased fatty acid metabolism. In addition, SCCs are more sensitive to inhibition of oxidative phosphorylation than to glucose deprivation, in vitro and in a murine xenograft model of GBM, and targeting both oxidative phosphorylation and the glycolytic pathway has a combinatorial inhibitory effect on GBM cell viability. These results demonstrate the presence of cellular subpopulations that exhibit distinct metabolic activities in GBM and highlight the importance of comprehensive metabolic inhibition in the novel GBM treatment strategies.

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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