

NFI –calcineurin – calpain – calpastatin pathway in MG cells which may regulate cell migration.

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**Lysosome disruptor's siramesine and the kinase inhibitor lapatinib induce synergistic cell death through ferroptosis in glioma cells**

*Gloria Elisa Villalpando Rodriguez, Anna Blankstein, Elizabeth S. Henson and Spencer B. Gibson. [spencer.gibson@umanitoba.ca](mailto:spencer.gibson@umanitoba.ca)*

Glioblastoma is inherently resistant to radiation and drug treatments. This is mediated by the most common forms of cell death are often actively inhibited. Identifying and exploiting alternative cell death pathways are essential to overcoming or bypassing drug resistance. Ferroptosis, a newly described, morphologically and biochemically distinct, cell death mechanism is characterized by iron-dependent cellular accumulation of reactive oxygen species. The combination of siramesine, a lysosome disruptor, and lapatinib, a dual tyrosine kinase inhibitor (TKI), synergistically induced death in glioma cancer cells. This cell death had characteristics of ferroptosis: it was blocked by the ferroptosis inhibitor ferrostatin-1 and the iron chelator deferoxamine. In addition, the amount of ROS and lipid peroxidation were increased in glioma cells. Iron transport protein remained unchanged but reactive iron levels increased. One target for kinase inhibitors is protein disulfide isomerase (PDI). Knockdown of PDI in combination with siramesine increased cell death that was blocked by ferrostatin-1. Taken together, drug combinations that alter reactive iron and ROS levels might induce ferroptosis and overcome drug resistance in glioma cells.

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**Prognostic significance of PD-L1 expression in meningioma for tumor recurrence; associated with hypoxia and NFKB2 activation**

*Shirin Karimi, Suganth Suppiah, Farshad Nassiri, Yasin Mamatjan, Jeff Liu, Gelareh Zadeh, Kenneth Aldape. [shirin.karimi@uhnresearch.ca](mailto:shirin.karimi@uhnresearch.ca)*

Estimation of tumor recurrence in meningioma patients is one of the important clinical challenges. The prognostic impact of immune modulatory molecule PD-L1 in several malignancies has been demonstrated. We studied the association of PD-L1 expression in meningioma with tumor recurrence and the underlying mechanism of its activation. Immunohistochemical staining (IHC) was performed for detection of PD-L1 and NFKB2 on whole sections of meningiomas diagnosed between 1998-2016 at Toronto Western Hospital. The biologic role of hypoxia in activation of PD-L1 in meningioma was investigated using gene set enrichment analysis (GSEA)-based on RNAseq data in validation cohorts. We analyzed a total of 93 meningioma cases: F/M ratio 58/35; WHO grade I(41), II(43), III(9), 42(47%) cases with tumor recurrence and median follow up was 6.97 yrs. PD-L1 expression on tumor cells (PD-L1TC) in 33(35%) cases was identified with distinctive patchy distribution. Univariate analysis

indicated expression of PD-L1TC as a prognostic factor for tumor recurrence ( $p < 0.0001$ ). Multivariate analysis showed that PD-L1TC expression is an independent prognostic factor for tumor recurrence after adjusting for extent of resection (EOR), WHO grade and maximum tumor diameter ( $p < 0.0001$ ). Analysis of RNAseq data of two GEOMeningioma studies demonstrated prominent expression of NFKB activation associated with PD-L1 expression. IHC analysis confirmed increased expression of NFKB2 protein in 26(30%) cases, which correlated with PD-L1TC expression ( $p = 0.02$ ). Furthermore, GSEA on a RNAseq data of 88 sporadic meningiomas using Hypoxia gene signature of HUVEC cells we found that the hypoxic sporadic meningiomas have significantly elevated PD-L1 expression ( $p < 0.001$ ). Our data strongly suggest that PD-L1TC expression serves as a significant prognostic marker for tumor recurrence and . We found that hypoxia and NFKB2 activation are potential underlying mechanisms. These results also provide a rationale for potential adjuvant therapeutic role for PD-L1 inhibitors in meningioma.

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**Does exercise improve progression free survival (PFS) and quality of life (QOL) in patients with glioblastoma? A trial in progress**

*Kim Edelstein, Kristin Campbell, Lori Bernstein, Ilyse Lax, Felicity Backhouse, Gregory Pond, Normand Laperriere, Barbara Ann Millar, David Shultz, Alejandro Berlin, Catherine Maurice, Gelareh Zadeh, Warren Mason [kim.edelstein@uhn.ca](mailto:kim.edelstein@uhn.ca)*

Background: Glioblastoma is the most common adult malignant glioma, with poor prognosis and adverse neurological sequelae. Physical activity improves outcomes in patients with other cancers, but has not been evaluated in GBM. This prospective, single-arm intervention trial examines feasibility and preliminary efficacy of exercise on PFS, cognition and QOL in newly diagnosed GBM patients. Method: Participants are English-speaking GBM patients scheduled for concurrent chemoradiation at PMH, 18-65 years old, ECOG  $\leq 2$ . The 3-month home-based exercise program includes aerobic and resistance training, tailored to prior fitness level, current physical status, and individual interests. Assessments of physical and neurocognitive functions, mood, fatigue, sleep, and QOL, occur within 2 weeks of starting chemoradiation, and approximately 3, 6, 12, and 18 months later, or until tumor progression. Feasibility will be assessed by accrual, retention, and adherence rates. Outcomes include PFS (RANO criteria), change in cognition (reliable change index method), physical activity and sleep (actigraphy, self-report questionnaires). Time-to-event outcomes will be estimated (Kaplan-Meier), and mixed modelling will explore individual and disease variables that contribute to outcomes. Results: During the first five months of recruitment, 13 of 19 eligible patients consented. Nine completed the exercise program. One patient died after the intervention and none of the others progressed. No exercise-related serious adverse events occurred. Preliminary results will be presented at the meeting. Discussion: Exercise appears feasible for GBM patients. Effects on survival, performance status, cognition, sleep, mood, and QOL are ongoing. Results may guide physical activity recommendations in GBM and generate avenues for translational research.