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Second Term Progress Report

Understanding temozolomide resistance in glioblastoma multiforme using a metabolomics-based approach

The general research objective is to understand the metabolic footprint associated with temozolomide (TMZ) treatment in glioblastoma multiforme (GBM), an aggressive and prevalent brain tumor. The median survival time for patients diagnosed with a GBM is between 12 to 15 months. Methylguanine DNA-methyltransferase (MGMT) is an enzyme that plays a significant role in TMZ resistance. MGMT removes the methyl group added by the alkylating agent TMZ and antagonizes its effects. This studentship helped the laboratory generate a TMZ-resistant U373 cell line (U373R) from TMZ-sensitive cells (U373S) to offer an additional model to study TMZ-resistance. Results obtained by crystal violet cytotoxicity assay indicate that there is a greater cell survival of U373R in comparison with U373S when treated with TMZ at 250µM. Furthermore, combination of lomeguatrib, an MGMT inhibitor, and TMZ treatment causes cell survival to be reduced in the resistant cell line. This reinforces the underlying involvement of MGMT in driving TMZ resistance in U373R. Metabolomics studies were used to assess the metabolic changes associated with MGMT inhibition, alone or in combination with TMZ, in TMZ-resistant and TMZ-sensitive GBM cells. Results notably show that citric acid cycle and glycolytic pathway intermediates such as aconitate, glucose, isocitrate and lactic acid are differentially regulated between the two cell models studied. These metabolites provide interesting starting points in the search of clinically-relevant biomarkers of TMZ resistance in patients diagnosed with a GBM. The search for such signature, in circulating as well as in primary tumor samples, will be undertaken in the upcoming year by leveraging key collaborations with local clinicians.

As a recipient of a Brain Tumour Research Studentship, I would like to express my sincere gratitude to the Brain Tumour Foundation of Canada for the great support that this scholarship has provided me. Besides the financial help associated with this award, the multiple biochemical and molecular biology techniques learned during the past two years, the various scientific presentations and publications I was involved with, as well as my overall research experience in Moncton has greatly influenced my decision to pursue a career in health research. Accordingly, I will be starting my master's degree in 2015. I feel privileged to have received such a prestigious scholarship and I will always be thankful to Brain Tumour Foundation of Canada for supporting my GBM-focused research project here in New Brunswick.

Scientific Conferences:

St-Coeur, P-D, **Poitras, J.J.**, Cuperlovic-Culf, M., Touaibia, M. and Morin, P. Jr**.** Novembre 2013, Montreal, Canada. Glioblastoma multiforme and temozolomide resistance: metabolic profiling as a diagnostic tool. CBGRC 16th Annual Chemistry and Biochemistry Graduate Research Conference. (Presentation)

Poitras, J.J., St-Coeur, P-D., Cuperlovic-Culf, M., Touaibia, M. et Morin, P. Jr. Mars 2014, Moncton, Canada. Compréhension et élucidation de la résistance au témozolomide chez le glioblastome multiforme. 25e Colloque des jeunes chercheuses et chercheurs. (Presentation)

Publication:

Cuperlovic-Culf, M., Touaibia, M., St-Coeur, P-D., **Poitras, J**., Morin, P. Jr., Adrian, S.C. (2014) Metabolic Effects of Known and Novel HDAC and SIRT Inhibitors in Glioblastomas Independently or Combined with Temozolomide. Metabolites, 4(3), 807-830.