Introduction: Glioblastoma (GBM) are characterized by enhanced migration and invasion abilities inherent to massive brain infiltration and hence abridged surgical resection. Together with their recognized treatment non-compliance, responses to standard therapy are invariably transient and recurrence is thus inevitable. Transforming Growth Factor-beta (TGF-b) is over-expressed and correlates with tumour aggressiveness. This cytokine heavily promotes invasion, proliferation as well as radioresistance of the tumour cells. We have already observed that treatment with chloroquine, a well-known antimalarial drug, produced important reduction in secretion of two TGF-b isoforms, TGF-b1 and 2.

Objective. Our objective was to assert the efficiency of chloroquine as to abrogate GBM invasion, proliferation and radioresistance. Results: In immortalized GBM cell lines (U-373 MG et U-87 MG) as well as in primary cultures from GBM patients, TGF-b inhibition halved glioma invasion measured in Matrigel-coated transwell invasion assays. Cell cycle analysis, immunofluorescence (against Ki-67 and cleaved caspase 3) as well as proliferation assays also show a 50% inhibition of the cell proliferation correlated with increases of apoptosis. Chloroquine treatment also radiosensitizes GBM cells as shown by an accumulation in the G2/M phase and increased cell death analyzed by flow cytometry. Discussion. We will confirm the radiosensitization effect of chloroquine with DNA damage analysis with TUNEL assays and gamma-H2AX immunofluorescence. Conclusion: These promising results suggest that using chloroquine to inhibit TGF-b might be an compelling therapeutic strategy and could benefit GBM afflicted patients.

Characterization of the chemoresistance profiles of malignant gliomas- A step towards a predictive individualized treatment

M-B Poirier, D Fortin

Department of Surgery; Faculté de Médecine et des Sciences de la Santé (FMSS), Université de Sherbrooke, Sherbrooke, Quebec

It is now a cliché to introduce malignant gliomas as aggressive tumours that remain incurable, despite decades of research. Median survival of patients bearing GBM remains 15 months with the current standard of care. Chemoresistance represents a significant problem, and only a subset of treated patients respond to chemotherapy. Among the chemoresistance mechanisms, the ABC transporters, expressed at the cell membrane of glial cancer cells as well as at the BBB and BTB, represents a clear impediment to chemotherapy efficacy. These efflux pumps purge the chemotherapeutic agents out of the cancer cells and out of the CNS. The overexpression of these proteins could also explain the emergence of resistance. We thereby undertook the analysis of the expression profile of MDR1, MRP1, MRP3 and BCRP, in a population of 122 GBM patients locally operated and treated, and to study this expression as a clinical surrogate for chemotherapy response at first and second-line treatment, as well as survival. As recent studies have demonstrated that these ABC transporter proteins display an avidity to uptake standard chemotherapeutic agents such as doxorubicin, etoposide, and vincristine as substrates, as well as the new class of small inhibitors of the tyrosine kinase receptor such as Imatinib, Erlotinib, and Gefitinib, the relevance of conducting an extensive characterization of their expression profiles is all too obvious. Results will be compared to the expression in normal samples (n=10) obtained through the Douglas Hospital, Montreal.

SP4

doi:10.1017/cjn.2014.73

PRDX1 as a radiosensitization target in ATRT

T Bader, L Lin, T Thanasupawari, T Klonisch, W Wang, J Pu, HD Sun, P McDonald, M Del Bigio, M Issaivanan

1Oncology and Cell biology, Manitoba Institute of Cell Biology; 2Department of Human Anatomy and Cell biology, University of Manitoba; 3Kunning Institute of Botany, Chinese Academy of Sciences; 4Department of Neurosurgery, University of Manitoba; 5Department of Pathology, University of Manitoba, Winnipeg

Purpose/Objective: Atypical teratoid rhabdoid tumors (ATRTs) are rare central nervous system tumors occurring exclusively in infants and children. Radiation is an important component of treatment. The overall prognosis of ATRTs is extremely poor with median survival of 10-18mths from the time of diagnosis. Peroxiredoxin 1 (PRDX1) is a thiol-dependent antioxidant enzyme that is over-expressed in multiple cancers. PRDX1 is also a cancer biomarker with over expression indicating advanced disease, increased angiogenesis, metastasis and poor outcome in several cancers. Down regulation of PRDX1 has been shown to have radio-sensitizing effects in lung cancer and other tumors. We investigated role of PRDX1 as a radio-sensitization target in ATRT. Methods: Gene expression analysis was done to find out the expression levels of PRDX1 in ATRT. We used siRNA transfection to knock down PRDX1 expression in primary ATRT cell lines BT-PA1 and BT-12/BT-16. A small molecule inhibitor (Adenanthin) was used to inhibit the activity of PRDX1. An MTS assay was used to evaluate radio-resistance after irradiation. The protein expressions were analyzed with immunoblotting. Results: PRDX1 is over expressed in ATRT cell lines similar to Group-3 Medulloblastoma cells. This was confirmed by both gene expression profiling and protein levels. Down regulation of PRDX1 by siRNA sensitizes ATRT cells to irradiation. Adenanthin inhibition of PRDX1 also caused similar radiosensitization comparable to siRNA knockdown. Conclusions: PRDX1 plays a role in radio-resistance in ATRT tumors. Adenanthin is a selective PRDX1 inhibitor. Further in vitro/ in vivo studies are required to validate PRDX1 as a potential radio-sensitization target in ATRT tumors.

SP3

doi:10.1017/cjn.2014.72

Characterization of the chemoresistance profiles of malignant gliomas- A step towards a predictive individualized treatment

M-B Poirier, D Fortin

Department of Surgery; Faculté de Médecine et des Sciences de la Santé (FMSS), Université de Sherbrooke, Sherbrooke, Quebec

It is now a cliché to introduce malignant gliomas as aggressive tumours that remain incurable, despite decades of research. Median survival of patients bearing GBM remains 15 months with the current standard of care. Chemoresistance represents a significant problem, and only a subset of treated patients respond to chemotherapy. Among the chemoresistance mechanisms, the ABC transporters, expressed at the cell membrane of glial cancer cells as well as at the BBB and BTB, represents a clear impediment to chemotherapy efficacy. These efflux pumps purge the chemotherapeutic agents out of the cancer cells and out of the CNS. The overexpression of these proteins could also explain the emergence of resistance. We thereby undertook the analysis of the expression profile of MDR1, MRP1, MRP3 and BCRP, in a population of 122 GBM patients locally operated and treated, and to study this expression as a clinical surrogate for chemotherapy response at first and second-line treatment, as well as survival. As recent studies have demonstrated that these ABC transporter proteins display an avidity to uptake standard chemotherapeutic agents such as doxorubicin, etoposide, and vincristine as substrates, as well as the new class of small inhibitors of the tyrosine kinase receptor such as Imatinib, Erlotinib, and Gefitinib, the relevance of conducting an extensive characterization of their expression profiles is all too obvious. Results will be compared to the expression in normal samples (n=10) obtained through the Douglas Hospital, Montreal.