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NEUROSCIENCE GRAND ROUNDS

Reversing temozolomide resistance in recurrent Glioblastoma multiforme (GBM): translating DNA repair biology research findings into new clinical interventions

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Speaker

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BIO

My research is focused on DNA damage and repair in neuro-oncology and CLL. I am a CIHR- and TFRI-funded Associate Professor within the Department of Pharmacology and Therapeutics (D-PT), a Senior Scientist within CCMR and Director of the Manitoba Tumour Bank. I was the recipient of the CIHR Institute of Cancer Research 2014 Early Career Award in Cancer Research and a CIHR New Investigator award. I have also established industrial partnerships, which have facilitated the development of innovative methodological platforms to accelerate my DNA damage repair research program. These were instrumental in obtaining my CFI JELF award to develop an innovative high-throughput genotoxicity and drug screening facility to interrogate DNA repair biology and to identify new therapies against neurological and lymphoproliferative malignancy. With this platform in-hand and my research program maturing, I was awarded a TFRI Terry Fox New Investigator Award to study deficiency/hyperactivity of DNA damage repair pathways underpinning resistant/recurrent disease. In total, I have garnered over $3.9M in funding from various local and international funding agencies including CIHR, CFI, Research Manitoba, CCMF and the Terry Fox Research Institute. I have published 39 peer-reviewed journal articles, book chapters and/or reviews. This body of work has garnered over 1500 citations and accrued an h-index of 18

OBJECTIVES

1. Review current challenges and mechanisms of treatment resistance in GBM

2. Present fundamental research findings using surgically resected primary GBM (pGBM) cells indicating a new biomarker underpinning a subset of resistant/recurrent GBM (rGBM)

3. Introduce new therapeutic avenues to resensitize rGBM to temozolomide

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RESEARCH

Glioblastoma multiforme (GBM) is a highly aggressive form of brain cancer that can afflict individuals of all ages. While rare, these tumours are responsible for a significant amount of malignancy-related morbidity and mortality. GBM treatment usually involves surgical resection of the tumour followed by radiation and chemotherapy (typically temozolomide, TMZ); however, GBM prognoses are generally poor and rarely curable due to tumour recurrence and a lack of effective treatments and surgical options. As such, there is a critical requirement to improve upon current anti-GBM therapeutic strategies.

Chemotherapeutic agents have multiple mechanisms of action, but primarily exert their anti-tumor activities via pervasive DNA damage that overwhelms the cellular DNA repair capacity resulting in cell death. We have developed novel TMZ-resistant cell models and an innovative high-throughput DNA damage analysis platform; combined these led to the discovery that persistent TMZ treatment stabilizes XRCC1 (an essential gene) and enhances PARP/XRCC1-dependent DNA base excision repair (BER). Our findings have been confirmed in a cohort of patient-derived recurrent GBM (rGBM) brain tumour initiating cells (BTICs); thus implicating XRCC1 as a TMZ drug-resistance factor underpinning recurrent GBM. Furthermore, our data suggests that hyperactive XRCC1-mediated DNA repair capacity promotes cross-resistance to second line DNA damaging chemotherapeutics, including radiation and Topoisomerase poisons.

We hypothesize that XRCC1 is a novel targetable biomarker for the resensitization of subsets of rGBM to TMZ treatment.

Primary Aims are to:

1. Establish XRCC1 as a clinically-relevant biomarker for TMZ-resistant/recurrent GBM. We have validated TMZ-mediated XRCC1 stabilization in several live patient-derived BTIC cell lines; however, we will interrogate XRCC1 expression in over 40 surgically-derived patient-matched primary and recurrent GBM tumors which have already undergone genomic, transcriptomic and proteomic cataloguing. As GBM patients usually remain on TMZ throughout their treatment course post-irradiation and into recurrence, overexpressed XRCC1 may serve as a biomarker of augmented BER activity that enhances resolution of TMZ-mediated DNA damage in a subset of these tumors.

2. Develop novel pharmacological inhibitors of XRCC1 to re-sensitize and ablate rGBM in vivo. Patient-derived primary BTICs will be interrogated with unique BER inhibitors to resensitize rGBM to TMZ. Amongst these include a clinical-grade PARP inhibitor (PARPi) that crosses the blood-brain-barrier and a novel XRCC1 inhibitor (XRCC1i) that we have recently identified. Our initial in vitro analyses of TMZ-resistant cell models and patient derived BTICs reveals significant synergism and/or TMZ re-sensitization following co-treatment with BER inhibitors. In vivo drug studies will be used to compare GBM patient-derived xenografts that express XRCC1 normally to those that feature XRCC1 overexpression following TMZ challenge.

Significance

The establishment of XRCC1 as a biomarker of TMZ-resistance may be a provocative precision-medicine approach in utilizing targeted anti-BER therapy to guide rGBM treatment and patient care. The findings of this study may be a significant milestone in fighting this otherwise deadly and incurable disease.

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