Brain Tumour Foundation of Canada Summer Studentship Final Report and Personal Statement

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Final Report

Over the past two summers at Dr. Katyal's lab, I have investigated the role of Topoisomerase I (Top1) in glioblastoma multiforme (GBM) brain cancer, the deadliest and most common brain cancer in the world. Top1 is a protein that relaxes strained DNA by generating transient single-strand nicks. My project focused on whether deliberate disruption of Top1 and its closely related cousin, Top2, by Top1/2 poisons like camptothecin (CPT) and etoposide can induce DNA damage and cell death in aggressive brain tumours like GBM.

I first determined changes in protein expression in 7 Top1 knockdown (shTop1) GBM cell lines and found, in all but one cell line, increased expression of both DNA double-strand break repair proteins and Top2. I then characterized the DNA integrity of these shTop1 cells and found increased DNA damage compared to the control. Examining the effects of Top1 loss on cell growth and sensitivity to Top1/2 poisons, I also found that shTop1 cells grew significantly slower than regular GBM cells and showed greater resistance to CPT treatment. Finally, I found that shTop1 cells where Top2 was upregulated upon Top1 loss showed increased sensitivity to etoposide, while conversely the shTop1 cell line where Top2 was not induced showed decreased sensitivity.

These findings point to differences in Top2 induction in GBM that may affect the sensitivity of tumours to Top1/2 poisons. For GBM patients, this means greater care must be taken to characterize the cancer before deciding on treatment. Better characterization would allow those patients with the right Top1/2 induction profile to use a combination treatment that may have greater efficacy than current therapies. Moving forward, my lab would like to investigate the mechanism of Top1/2 interaction, specifically if Top2 induction is connected to Top1 loss by DSB repair proteins. Understanding this mechanism would provide more targets for novel chemotherapies, and most importantly help to improve the efficacy of current ones.

Personal Statement

With the opportunity provided by this studentship, I have experienced many facets of the process of scientific discovery, from the satisfaction of successful experiments and promising data to an appreciation of the intellectual integrity that makes research reliable and reproducible. This studentship has given me more insight into the everyday business of scientific research.

I definitely plan to incorporate research into my career, and I hope it will continue to be in the field of brain tumours. Knowing that I might have an opportunity to fight such a deadly disease, in both the clinic and the lab, motivates me to make such a career a reality. Thank you to the Brain Tumour Foundation of Canada, and the donors, for giving me such a valuable experience.