Brain Tumor Foundation of Canada Final Report

Project Summary

Biallelic Mismatch-Repair Deficiency (bMMRD) is a cancer predisposition syndrome characterized by childhood onset of multiple cancers including brain and colorectal cancers. bMMRD patients are born with mutations in mismatch repair genes. There is an adult-onset counterpart of bMMRD syndrome termed Hereditary Nonpolyposis Colorectal Cancer (HNPCC), which occurs in adults carrying mutations in the same mismatch repair genes.

The well-validated diagnostic hallmark of HNPCC is the presence of expansions and contractions of repetitive DNA sequences in tumour cells, termed Microsatellite Instability (MSI). Curiously, patients with bMMRD syndrome do not consistently display MSI. Our genomic analysis of 8 microsatellite markers in 12 bMMRD tumours and 10 normal bMMRD tissues corroborated this inconsistence.

To clarify MSI expression in normal and cancerous cells of bMMRD patients, we conducted conventional MSI testing on 38 bMMRD samples. 26% (10 of 38) bMMRD tumours displayed MSI. MSI was more frequently expressed in certain tissues: only 10% of brain tumours displayed MSI, relative to 44% and 100% of colorectal polyps and tumours respectively. Using novel genomic technologies, we then performed MSI testing on single-cells derived from bMMRD normal tissues. We showed that MSI can be detected in bMMRD single-cells: between 6 to 23% of cells tested displayed MSI. The low frequency of MSI expression in bMMRD cells could explain why conventional diagnostic techniques fail to capture MSI in bMMRD samples.

Next steps for this research include investigating the tissue-specific nature of MSI, isolating the effect of specific mutations on MSI expression, and examining the change in MSI expression over time in bMMRD cells.

Diagnosing bMMRD syndrome is currently complicated by variable clinical presentation and difficulties performing genetic sequencing. As the first study to identify MSI in bMMRD single-cells, the novel genomic technologies employed in this study could be adapted into a diagnostic tool for bMMRD syndrome. Swift and accurate diagnosis of bMMRD patients is important for surveillance and treatment considerations.

Impact of award

The research that I had the opportunity to conduct in Dr. Uri Tabori's lab because of the Brain Tumour Foundation of Canada's Research Studentship award sparked my interest in a career as a clinician-scientist. I particularly enjoyed the challenges of basic science research delving into the molecular intricacies of brain tumour development. At the same time, I was driven by the promise this research holds for improving outcomes for brain tumour patients. As a result, I applied for, and was successful in my application to McGill University's MD-PhD program. I will be continuing in the field of brain tumour research as a PhD student in Dr. Nada Jabado's lab, investigating the role of epigenetics in the development of pediatric brain tumours.

Publications

Shlien A, Campbell BB, de Borja R, et al. Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. *Nature Genetics*. 2015.

Presentations

1. Brain Tumour Foundation of Canada National Conference – Join the Movement to End Brain Tumours – Abstract/Poster Presentation (October 2016)
2. Institute of Medical Science Summer Undergraduate Program Annual Day – Abstract/Poster Presentation (August 2015)
3. SickKids Summer Research Program - Abstract/Poster Presentation (August 2014)

Awards

Canadian Psychological Association - 2015 Certificate of Academic Excellence (for Honours Thesis)