Leveraging a Data-Sharing Infrastructure for Pan-Cancer Circular RNA Profiling and Clinical Validation

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Background and rationale: Most of our genetic material produces RNA molecules that never become proteins. One intriguing type is circular RNA (circRNA) molecules that form closed loops. This unique feature makes them highly stable and in addition their presence in blood and urine, positions them as potential valuable non-invasive cancer markers. Previous work from our group in a Marathon of Hope Cancer Centres Network (MOHCCN) prostate cancer cohort identified over 25,000 high-confidence circular RNAs. Notably, patients with extreme levels of circular RNA production (either very high or very low) had significantly worse outcomes, suggesting these molecules can provide important clinical information beyond traditional markers. However, most large cancer databases cannot detect these molecules because standard sequencing methods specifically exclude them. The MOHCCN's specialized RNA sequencing preserves circular RNAs, providing a unique opportunity to study them in Canadian patients.

Objectives: The primary objective of this project is to create a comprehensive catalogue of circular RNAs across Canadian cancer patient samples collected through the MOHCCN. Specifically, we aim to: (1) develop and validate a computational pipeline to accurately identify and measure circular RNAs in patient tumour samples; (2) determine which circular RNAs are associated with patient outcomes, cancer subtypes, and treatment responses; and (3) identify circular RNAs that could serve as potential biomarkers or therapeutic targets.

Methods and Results: Our computational approach applies algorithms to identify the unique junctions that define circular RNAs. We identified thousands of high-confidence circular RNAs with patient-specific profiles across cohorts and cancer types. We will perform clustering to identify subtypes, calculate a score to quantify global production levels per patient, and conduct survival analyses to determine associations with patient outcomes. We will also examine relationships with clinical features such as tumour grade, stage, and treatment response.

Conclusions: The MOHCCN's sequencing data provides an unprecedented opportunity to study circular RNAs in Canadian cancer patients. Our analysis will generate the most comprehensive catalogue of cancer-associated circular RNAs in Canadian patients, filling a critical gap in our understanding.

Anticipated Impact: This research has direct implications for patients. Because circular RNAs are stable, they could serve as biomarkers detectable in blood or urine, enabling less invasive cancer monitoring. Understanding which circular RNAs drive cancer could reveal new therapeutic targets for RNA therapeutics. Associations between circular RNA patterns and outcomes could improve predictions of which patients need aggressive treatment. This publicly available resource will enable Canadian researchers to explore these molecules across cancer types, accelerating translation into clinical applications.