Identification and clinical implications of circular RNA in cancer

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Abstract

Background and rationale: While more than 75% of the human genome can be transcribed, only 1-2% is translated. Although these RNA transcripts that do not produce proteins termed noncoding RNA (ncRNA), consist of more than 80% of the RNAs from the human genome most of them remain poorly characterized. One understudied form of ncRNA is circular RNA (circRNA). Recent next-generation RNA sequencing (RNA-seq) has uncovered the widespread expression of these covalently closed single-stranded transcripts across cell and tissue types. Increasing evidence supports a major role of circRNAs during cancer initiation, progression, and outcome. Also, due to their production, distribution, and stability, circRNAs offer novel biomarker and therapeutic opportunities. CircRNAs lack polyA tails and are thus missed by polyA enrichment profiling in most clinical dataset including The Cancer Genome Atlas Program. The ribosomal RNA depleted (Ribo-) RNA-seq profiling of the MOHCCN cohorts provides a unique opportunity to identify clinically relevant circRNAs.

Objectives and research plan: The overall objective is to identify and quantify the abundance of circRNAs across the MOHCCN cohorts for the purpose of identifying novel circRNAs across cancer types and to determine their associations with clinical features, outcomes, and treatment response. The central **hypothesis** is that the deregulated circRNA expression patterns in cancer are associated with clinical features, treatment response and outcomes and have the potential to serve as biomarkers and therapeutic targets. In Aim 1, we will compile a circRNA analysis pipeline to identify and quantify circRNAs across MOHCCN cohorts. In Aim 2, we will leverage the clinical and genomic data to investigate how the high-confidence circRNAs identified are associated with clinical features, outcomes, and treatment response.

Integration with sponsoring program: The proposed project is in great synergy with the sponsoring program. The Ribo- RNA-seq of the MOHCCN cohorts provides a unique opportunity to identify clinically relevant circRNAs for biomarker and therapeutic target discoveries. We will investigate circRNAs across the MOHCCN themes, which will give us novel insights into cancer biology, biomarkers, mechanisms of drug resistance and risk stratification.

Innovation and anticipated results: No study to date has systematically investigated the role of circRNAs across the MOHCCN cohorts. Our study will provide unprecedented insight into the landscape of circRNAs which will be a new research frontier in cancer diagnosis, treatment, and outcome.

Plain language summary

Objective: Our objective is to analyze an understudied molecule called circular RNA (circRNA) to understand its involvement in how cancers start, grow and why certain patients respond less well to therapy.

Previous research: Researchers have long focused on how unexpected and permanent changes in our genetic makeup, or DNA leads to diseases like cancer. However, just looking at DNA might not be giving us the full picture. DNA has the vital information needed to maintain our bodies, but RNA is what does most of the work by reading and translating parts of DNA. While a large part of our genetic information can be read, only a small portion is translated into the molecules essential for life. Therefore, most RNAs exist as different types we broadly call noncoding RNA (ncRNA) that do not produce these molecules. Several types of ncRNAs have been found to be present in cancer and have different roles such as affecting how cancer cells respond to treatment and grow. One type of ncRNA is circRNA which has distinct properties and functions. Compared to most RNAs, circRNAs are very stable and specific to different tissues. There is also growing evidence of circRNAs being involved in cancer. Owing to their unique features, circRNAs have the potential to help in the detection of cancer and be targets for new therapies.

Project methods: We will first refine and apply a computational method to detect circRNAs in cancer samples from the Marathon of Hope Cancer Centres Network (MOHCCN) patient cohort data, followed by several analyses combining different kinds of additional data to investigate how the identified circRNAs influence these cancers.

Impact and relevance to cancer: While cancer research has long been focused on changes in the DNA, looking at changes in ncRNAs marks a shift in the field. To this end, understanding how circRNAs affect cancer initiation, progression and treatment response is vital to interpreting the full landscape of the disease.