Revealing colorectal cancer non-coding driver mutations in an isolated population with multi-omics

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Scientific Abstract

Newfoundland and Labrador (NL) provide a unique opportunity to study the biology of colorectal cancer (CRC) due to its genetically isolated population and unique environmental exposures. This combination of high hereditary and environmental factors has resulted in one of the highest CRC incidence rates in the world. Through our involvement in the Marathon of Hope Cancer Centres Network, led by the Terry Fox Research Institute via the Atlantic Cancer Consortium, we have generated preliminary genomics and transcriptomics data on a local cohort of colorectal cancer patients.

With this project, we aim to characterize non-coding pathogenic variants and mutations that disrupt gene regulation. Specifically, we focus on non-coding germline variants and somatic mutations located in regulatory elements such as promoters and enhancers.

To achieve this, we performed in-house Chromatin Immunoprecipitation followed by sequencing (ChIP-Seq) with colorectal tissue samples collected from local patients to target H3K27ac, a histone mark associated with active regulatory elements, including super-enhancers. By combining ChIP-Seq data with WGS and RNA-Seq, we provide a comprehensive view of the regulatory landscape in colorectal cancer, highlighting potential non-coding drivers of disease.

To date, a subset of six patients from the cohort have undergone whole genome sequencing (WGS; Illumina), RNA sequencing (RNA-Seq; Illumina) and H3K27ac ChIP-seq (Complete Genomics). These preliminary data indicate that genomic mutations are linked to epigenetic variations, which in turn are associated with changes in gene expression. Emerging evidence suggests that mutations in regulatory elements can either disrupt existing transcription factor binding sites or create novel binding sites, contributing to tumorigenesis. Our study integrates these findings with multi-omics data to identify population-specific genetic mutations and regulatory disruptions in NL's colorectal cancer patients.

Keywords: Colorectal cancer, enhancers, ChIP-seq, genetic mutations

Plain Language Abstract

Newfoundland and Labrador (NL) provide a unique opportunity to study the biology of colorectal cancer (CRC) due to its genetically isolated population and unique environmental exposures. This combination of high hereditary and environmental factors has resulted in one of the highest CRC incidence rates in the world. Through our involvement in the Marathon of Hope Cancer Centres Network, led by the Terry Fox Research Institute via the Atlantic Cancer Consortium, we have generated preliminary genomics and transcriptomics data on a local cohort of colorectal cancer patients.

With this project, we aim to characterize new impacts of mutation that can disrupt gene regulation. Specifically, we focus on non-coding germline variants and somatic mutations located in regulatory elements such as promoters and enhancers.

To achieve this, we sequenced DNA in the chromatin state from colorectal tissue samples collected from local patients to target H3K27ac, a histone mark associated with active regulatory elements, including super-enhancers. By combining our data with genomic and sequencing of RNA, we provide a comprehensive view of the regulatory landscape in colorectal cancer, highlighting potential non-coding drivers of disease.

The preliminary data indicate that genomic mutations are linked to epigenetic variations, which in turn are associated with changes in gene expression. Emerging evidence suggests that mutations in regulatory elements can either change transcription of DNA contributing to tumorigenesis. Our study takes this multi-source data to identify population-specific genetic mutations and regulatory disruptions in NL's colorectal cancer patients.