Characterizing the molecular and clinical landscape of BRAF-mutant colorectal cancer: toward the identification of novel therapeutic vulnerabilities

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Background and rationale: BRAF mutations arise in 15% of colorectal cancer however only about 25% of BRAF V600E mutant colorectal cancers respond to current therapies and there are no approved treatments for Non-V600E BRAF mutant colorectal cancers, thus prompting us to investigate the molecular makeup of these cancers.

Objective: Identify the clinical, genomic and transcriptomic profile of BRAF mutant colorectal cancers with large scale public databases

Methods & Results: We obtained clinical, genomic and transcriptomic data from 3 different public databases of colorectal cancers. Inclusion criteria were tumours with a classifiable BRAF mutation and patient age over 20 years old. RNA sequencing data was normalized and analyzed with appropriate software. We identified that Non-V600E BRAF mutations were more common in males, in younger patients and in metastatic sites. We did not observe differences in the MAPK pathway in these different BRAF mutant colorectal tumours although we found differences in immune pathways which were more active in tumours with V600 vs Non-V600E BRAF mutations. Multivariable Linear Regression analysis confirmed that this enrichment was not associated to MSI status of these tumours.

Conclusion: The enrichment of the immune pathway suggests that the BRAF V600E tumours may be more immunologically hot tumours and better suited for immunotherapies while the Non-V600E BRAF mutant tumours would be better suited for targeted therapies.

Pervasive early dissemination in pancreatic cancer uncovered by tissue-paired plasma whole-genomes

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In pancreatic cancer, 50% of the patients are diagnosed at the metastatic stage due to a lack of symptoms. The overall survival rate dramatically reduces from 44% in early-stage resectable patients to 3% in metastatic cases. However, even in early-stage patients, >75% of them still recur after resection and adjuvant therapies. Therefore, there is an urgent need to develop a sensitive strategy to detect this disease earlier before it spreads. Characterizing circulating tumor DNA (ctDNA) in plasma is an effective approach to detect and monitor cancer. Whole-genome sequencing (WGS) tracks all the tumor mutations simultaneously, and has a higher sensitivity than targeted approaches, especially in samples with extremely low tumor burden. In this study, to investigate the ctDNA dynamics and early dissemination in pancreatic cancer, we established a cohort of 1,013 samples from 277 donors, including plasma WGS at 20-60x, alongside germline DNA WGS, tissue WGS and transcriptomic sequencing. Using a tumor-guided approach, we found that the early-stage resectable cases shed very little ctDNA (<1% tumor fraction, TFx). Plasma TFx levels were elevated at the metastatic stage, but were also dependent on metastatic tissue site, where patients with liver metastases had higher TFx than the ones with only non-hepatic lesions. We further discovered the tumor-intrinsic features that were related to increasing ctDNA shedding, such as whole-genome duplication (WGD), high cell cycle activity and non-glandular morphology, as well as extrinsic features related to reduced shedding, including a reactive microenvironment and B cell immunity. Our analysis on tumor clonal architecture revealed that subclonal mutations were more frequently detected than the clonal ones in plasma samples with low ctDNA levels or from early-stage patients, which strongly suggests that dissemination from early-stage primary tumors mostly derived from subclones. In the longitudinal plasma, we observed that subclones seeded metastasis years before imaging diagnosis. This study with a unique large cohort of paired tumor and plasma sequencing data provided a comprehensive insight on ctDNA dynamics, disease monitoring and early detection in pancreatic cancer.

Decoding Epithelial Plasticity: Exploring the Influence of SWI-SNF Complex Mutations on Bladder Cancer Progression

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Background and Rationale: The majority of bladder cancers are diagnosed at early stages, respond well to frontline immunotherapy and have great survival outcomes. However, in 10–30% of patients, the disease progresses to a more aggressive form following initial treatment, invading into and beyond the muscular layers of the bladder. These aggressive cancers often lose the features of normal bladder cells and instead adopt a more primitive, stem-cell-like state that allows them to grow, spread, and resist therapy.
Low oxygen levels are common inside tumours and are known to trigger stress responses that promote this aggressive stem-cell-like behaviour. Notably, genetic mutations in the SWI-SNF complex, which are abundant in bladder cancer, have been shown to increase the sensitivity of tumour cells to these low-oxygen conditions and promote disease progression. While similar processes have been described in other cancers, their role in bladder cancer progression has remained unclear.

Objectives: The goal of this study is to determine how bladder cancers with SWI-SNF complex mutations evolve in low oxygen conditions to drive tumour aggressiveness, disease progression, and poor patient outcomes. Further, the study aimed to identify measurable markers of aggressive disease and evaluate potential strategies to inhibit this process.

Methods and Results: We analyzed large, publicly available bladder cancer datasets to examine how genetic mutations, tumour oxygen levels, and patient outcomes are related. We found that tumours carrying specific mutations in the SWI-SNF complex and showing strong low-oxygen responses were significantly more likely adopt an aggressive stem-cell-like identity and were associated with worse overall survival.
Laboratory experiments showed that when bladder cancer cells were deprived of oxygen, they activated stress responses and lost features of normal bladder cells, adopting behaviours commonly associated with tumour progression in bladder cancer.
Finally, analysis of intact patient tumour samples showed that markers of low oxygen, cellular stress, and aggressive behaviour were spatially clustered within the same tumour regions, confirming that these processes are co-occurrent in bladder tumour tissues.

Conclusions: This study demonstrated that low oxygen levels and SWI-SNF complex mutations work together to drive bladder cancers toward a more aggressive and treatment-resistant state. This process helps explain why some early-stage bladder cancers progress rapidly despite standard treatment.

Anticipated Impact: These findings have important implications for bladder cancer patients. The identified molecular markers could be developed into tests to identify high-risk patients earlier, allowing for closer monitoring and more timely intervention. In addition, the study highlights targetable systems that could prevent tumours from becoming aggressive, offering the potential to improve survival and quality of life for patients with bladder cancer.

Background and rationale: Synthetic lethality is a phenomenon where the simultaneous occurrence of genetic abnormalities in two or more genes leads to cell death while their presence individually does not affect cell viability. It introduces a new approach for anticancer therapeutics by exposing genetic vulnerabilities in tumor cells that can be targeted without harming normal healthy tissue. Although there is increasing evidence that supports the biomarker and therapeutic potential of synthetic lethal interactions, clinical translation is hindered by the lack of ready-to-use frameworks for synthetic lethal investigations and rigorous validation of published biomarkers.

Objective: Our objective is to facilitate clinical applications of synthetic lethal biomarker detection and assess their robustness across independent datasets.

Methods and Results: We created a computational framework for identifying synthetic lethal biomarkers from patient mutation and gene expression profiles. Published synthetic lethal biomarkers were extracted from SynLethDB and validated using cell line gene essentially scores. We applied our computational framework to 731 patients across eight MOHCCN cohorts. Single knock-outs of at least one synthetic lethal pair were detected in 652 patients (89.2%), of which 557 patients (76.2%) harbored at least one druggable synthetic lethal pair. Validated pairs successfully stratified cell lines by therapeutic response to corresponding targeted agents.

Conclusions: Our findings demonstrate widespread prevalence of targetable synthetic lethal vulnerabilities across diverse patient populations and provide evidence supporting a new paradigm of biomarker-driven patient stratification in precision oncology trials.

Anticipated Impact: By systematically prioritizing synthetic lethal pairs for functional validation, new biomarkers can expand the population of patients eligible for targeted therapeutic interventions. Our open-source, quantitative framework will also provide a robust platform for accelerating synthetic lethality research and clinical translation, with potential to transform patient selection strategies in oncology.

Defining the genomic and immunologic landscape of colorectal cancer.

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Background and rationale: Colorectal cancer (CRC) is a major cause of cancer and death in Canada, especially in the Atlantic provinces. Treatment responses depend on the genetic characteristics of a person's tumor and the action of the immune system. For successful treatment, the immune system must remove the tumour cells that chemotherapy and surgery miss. In this project, we are partnering with physicians to study how the immune response is related to tumor genetics and patient clinical characteristics.

Objective: We are using innovative technology to study both the types of immune cells within CRC, and how they interact with each other and tumour cells. We will compare these patterns considering tumor genetics and patient clinical characteristics.

Methods and results: Tumor samples from patients treated between 1997-2009 were studied using fluorescence microscopy which allows the identification of several types of immune cells at the same time. Images from our samples were processed with computer analysis to identify individual cell's characteristics and their localization and organization in tumors. We found that patients with high numbers of $CD94^+$ killer T cells and $CD16^+$ natural killer (NK) cells, two cell types which can kill cancer cells, had longer survival. Patients whose tumor's had both cell types, had longer survival than patients with either cell type alone.

Conclusions: Our findings suggest that cooperation of $CD94^+$ killer T cells and $CD16^+$ NK cells may improve their cancer cell killing capacity as seen by longer patient survival. Now, we are doing more experiments to understand the specific features of them, and how they communicate.

Anticipated Impact: We expect that understanding the function and characteristics of these cells could inform pathways for improved immunotherapies. We hope that, in the future, genetic testing will allow doctors to prescribe treatments as precisely as possible for each patient.

Title: Using Natural Language Processing to Verify Variant Interpretation Data in Precision Oncology

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Background and Rationale: Advances in cancer genomics have enabled treatment decisions to be tailored to the specific genetic alterations present in an individual patient's tumor. This approach, known as precision oncology, relies on accurate interpretation of how genetic variants influence cancer biology, prognosis, and response to therapy. However, the evidence supporting these interpretations is spread across an increasingly large and complex biomedical literature, making it difficult to assess, verify, and maintain consistently over time.

To address this challenge, the oncology community relies on curated knowledge bases, structured resources that summarize evidence from published studies into clinically meaningful interpretations. One prominent example is CIViC (Clinical Interpretation of Variants in Cancer), an open, expert-curated knowledge base that links cancer-related genetic variants to specific claims about their biological or clinical significance, together with supporting literature. While such resources are essential for bridging research and clinical practice, their accuracy depends on continuous expert review, which has become a major bottleneck as the volume of relevant literature continues to grow.

Objective: The objective of this study is to assess whether modern artificial intelligence (AI) systems, specifically large language models, can help scale the verification and review of scientific claims used in cancer variant interpretation knowledge bases.

Methods and Results: We developed CIViC-Fact, a benchmark dataset designed to evaluate automated fact-checking in a realistic biomedical context. CIViC-Fact links structured variant interpretation claims to specific sentences in full-text research articles that either support or contradict those claims, closely reflecting the evidence assessment tasks performed by expert curators.

Using this dataset, we evaluated the ability of language models to determine whether published evidence substantiates a given claim. The results show that these models can effectively identify supported claims and flag cases where evidence is insufficient or inconsistent. Importantly, the models are used to assist, rather than replace, expert review by enabling preliminary screening and prioritization.

Conclusions: AI-assisted fact-checking can augment expert-driven cancer variant interpretation by improving the efficiency and consistency of evidence verification while preserving human oversight and judgment.

Anticipated Impact: By helping experts manage the growing biomedical literature more efficiently, AI-assisted fact-checking has the potential to keep cancer knowledge bases more accurate and up to date. For cancer patients, this supports greater confidence that genomics-informed care decisions are based on current and reliable scientific evidence. More broadly, this work provides a framework for responsibly integrating AI into biomedical knowledge curation to help translate research advances into improved cancer care.

DeepTumour: Enhancing an advanced algorithm for tumour origin identification

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Background and Rationale: Knowing where a tumour starts in the body and what type of cell it comes from is essential for choosing the right treatment. Current diagnosis relies on examining tumour tissue under a microscope, but this approach has limitations. Different tumours can look alike, and tumours can change as they grow and spread. As tumours form, cancer cells acquire DNA changes that leave molecular "footprints" reflecting where the tumour began. Our team previously used these patterns from tumour tissue samples to develop DeepTumour, which identifies 24 common tumour types with high accuracy.

Objective: This project explores whether DeepTumour can be applied to blood samples, which carry small pieces of tumour DNA from dying cancer cells.

Methods and Results: Blood samples contain much less tumour DNA than tissue samples, which limits the information available for analysis. Because large blood-based datasets are not yet widely available, we trained the model using tumour tissue data from approximately 2,600 samples. To mimic the lower amount of tumour DNA found in blood, we kept only a portion of each patient's DNA mutation information. Using this approach, the model was expanded to identify 29 tumour types with 90% accuracy. It maintained over 78% accuracy when trained and evaluated with only 25% of the mutation data. When tested on real blood samples from 178 pancreatic cancer patients, the model achieved 76% accuracy.

Conclusion: This study shows that DeepTumour can potentially be adapted for blood-based analysis while maintaining reliable performance.

Anticipated Impact: This work supports the development of a minimally invasive research tool that could help classify tumours when tissue samples are unavailable or inconclusive.

MULTi-modal Integration in Pancreas cancer using machine Learning (MULTIPL): Personalized predictions of outcomes across the spectrum of disease and treatments

David Henault

Background and rationale:

For people with advanced pancreatic cancer, chemotherapy is usually the main treatment. Two commonly used first options can work, but not for everyone—and today, doctors often have to choose a treatment without a reliable way to predict which one will help a specific patient the most. A tool that could better "match" patients to the most effective chemotherapy from the start could save precious time and avoid unnecessary side effects.

Objective:

To build and test a computer-based prediction tool (an AI algorithm) that uses information from a patient's cancer and routine clinical data to help guide the initial choice of chemotherapy.

Methods and Results:

We trained our algorithm using patient data from one large pancreatic cancer research study (COMPASS). We then tested it on a completely separate group of patients from another study (PASS-01), to see if it still worked well on new patients it had never "seen" before.

Among the different models we developed and tested, the best one was MULTIPL (late fusion) – a version that combines several sources of information to make a single prediction.

Conclusion:

Our results suggest that MULTIPL can make meaningful predictions on an independent dataset, which is an important step toward a tool that could support more personalized treatment decisions.

Anticipated impact:

With further validation, this approach could help identify the most suitable first chemotherapy right away, improving the chance of benefit and reducing trial-and-error. This tool is meant to support (not replace) shared decision-making between patients and their care team, and it will require additional testing before routine clinical use.