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Role of gut and intratumoural microbiota on response to immune checkpoint inhibitors in lung cancer and melanoma

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Abstract:

Background and rationale:
The gut microbiome is now considered a hallmark of cancer and a key determinant of response to immune checkpoint blockade (ICB). As a result, several strategies are underway to change the gut microbiome in patients with non-small cell lung cancer (NSCLC) and melanoma, including ongoing and planned clinical trials using fecal microbiota transplantation (FMT). However, an emerging and still controversial field regarding the role of the tumor microbiome in ICB activity remains unknown. Therefore, this project seeks to define the tumor microbiome and its relationship to other clinical features including tumor immune microenvironment and response to ICB.

Objectives:
1) To understand the role of the gut microbiome in modulating response to ICB using fecal microbiota transplantation in clinical trials and to uncover genomic biomarkers of response to fecal microbiota transplantation with ICB
2) To characterize the intratumoral microbiome in patients treated with immune checkpoint blockade; and to determine the role of the intratumoral microbiome on response to ICB and its impact on the tumor microenvironment
3) To understand the relationship between the gut microbiome and the intratumoral microbiome

Research Plan: A clinical trial evaluating fecal microbiota transplantation plus ICB is currently underway (NCT04951583) in patients with NSCLC and melanoma amenable to first-line ICB. Gut microbiome sequencing will be characterized using shotgun metagenomic sequencing. Tumors will be sequenced using whole genome and transcriptome sequencing. Bacterial genomic content will be assessed by mapping of off-target reads to the NCBI database. Gut and tumor microbiome features will be associated with response to ICB plus fecal microbiota transplant. In addition, additional fresh tumors will be cultured and subjected to 16s rRNA sequencing from patients enrolled in our lung and melanoma biobanks with matching stool samples available to correlate the gut and tumor microbiome with intratumoral features including tumor immune microenvironment and clinical outcomes.

Anticipated Results and Impact: In addition to evaluating a new therapeutic strategy employing fecal microbiota transplantation in combination with ICB to improve ICB activity, this project will characterize the tumor microbiome and its connection with the gut microbiome and tumor microenvironment.

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Plain language summary:

Background and rationale

Lung cancer and melanoma remain the leading cause of cancer-related death and leading cause of skin cancer-related death in Canada, respectively. Immunotherapy trains the immune system to kill cancer cells and is the most common therapy for lung cancer and melanoma. Unfortunately, the majority of patients experience cancer growth despite immunotherapy. Bacteria living in the intestine (gut microbiome) and living in lung and melanoma tumors (tumor microbiome) and influence immunity and potentially the response to immunotherapy. Our project is working to test whether fecal microbiota transplantation—a treatment already approved for C. difficile colon infection—can improve cancer immunotherapy activity. A new and controversial field regarding the tumor microbiome may also be important in determining which patients will respond to immunotherapy. Therefore, this project seeks to define the tumor microbiome and its relationship to other markers in the tumor and response to immunotherapy.

Objectives

1) To understand the role of the gut microbiome on response to immunotherapy by evaluating the role of treatment with fecal microbiota transplantation in combination with immunotherapy in a clinical trial of patients with lung cancer and melanoma
2) To define the types of bacteria, present in lung and melanoma tumors treated with immunotherapy and to determine the role of these bacteria on response to treatment
3) To understand the relationship between the gut microbiome and the tumor microbiome

Research plan

A clinical trial evaluating combination fecal microbiota transplantation with immunotherapy is currently ongoing in patients with lung cancer and melanoma. We will measure the different bacteria in the gut and tumor using sequencing. We will also culture tumors to see if bacteria grow in culture. We will compare the make-up of the gut microbiome to the tumor microbiome and connect these findings with immune cells present in the tumor and the response to immunotherapy.

Anticipated Results and Impact

In addition to evaluating a new treatment in patients with lung cancer and melanoma to improve response to immunotherapy using the gut microbiome, this project also aims to understand the relationship between the gut and tumor microbiome and how it influences the response to cancer immunotherapy. We anticipate that these results will provide new ways to improve immunotherapy effectiveness in patients with lung cancer and melanoma.