High fiber diet modifies gut microbiome, propionate production, intratumor immune response and is associated with outcome in patients with lung cancer treated with immune checkpoint inhibitors

Corentin Richard*, Myriam Benlaifaoui, Omar El Quazzadi, Khoudia Diop, Antoine Desilets, Julie Mâlo, Wiam Belkaïd, Andréanne Leblanc, Julien Lamontagne, Meriem Messaoudene, Arielle Elkrief, Bertrand Routy. CRCHUM, Montreal, Canada

Background The gut microbiome plays a key role in immune checkpoint inhibitors (ICI) efficacy and several strategies are currently being investigated to improve microbiome composition. The impact of a specific diet on microbiome modulation and clinical outcomes remains unknown. In this study, we assessed the effects of a high fiber diet on clinical outcomes as well as on microbiome composition, production of fecal metabolites, and intratumor immune infiltration in metastatic non-small cell lung cancer (mNSCLC) patients amenable to ICI.

Methods In this prospective study, 39 chemotherapy-refractory or naive patients with mNSCLC treated with ICI alone or in combination with chemotherapy completed a validated dietary survey. Based on the total fiber intake, patients were divided into high vs low fiber groups (HF vs LF). Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were compared between both groups. In addition, fecal and tumor samples were collected prior to ICI initiation. Fecal metagenomic sequencing was performed and fecal short-chain fatty acids (SCFA) were measured by LC-MS/MS. Tumor transriptome profiling was performed through RNA sequencing to define differentially expressed pathways.

Results Baseline characteristics were well balanced between both groups, including body mass index (BMI) and PD-L1 status. Median PFS for the HF group was longer compared to the LF group (27.4 vs 12.6 months). Microbiome metagenomic profiling revealed higher baseline alpha diversity (p=0.048) in the HF group compared to the LF group. Bifidobacterium, Alistipes, and Bacteroides salyersiae were enriched in the HF group while Fusobacterium was overrepresented in the LF group. SCFA measurement revealed that a high level of propionate correlated with a significantly longer OS (not reached vs 18.4 months, p=0.02) in the entire cohort. Moreover, propionate levels were significantly higher in the HF vs LF group (p=0.02). At the tumor level, RNA sequencing demonstrated a downregulation of DNA repair mechanisms and an upregulation of humoral and adaptive immune responses in the HF group.

Conclusions In this study, we demonstrated that a HF diet in patients with mNSCLC was associated with better clinical outcomes. Importantly, HF was associated with an enrichment of previously reported beneficial gut bacteria. Moreover, propionate correlated with longer OS and was increased in the HF group. This study provides further insights into how the diet can beneficially shift the microbiome composition and intratumor immune responses in patients with mNSCLC treated with ICI and this may lead to novel, dietary-geared therapeutic avenues in the oncomicrobiome arena.

Ethics Approval The study was approved by CRCHUM Institution, Ethics Board, approval number 17.035.

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gastrointestinal and auto-immune disorders. This assay performs at 100% sensitivity and specificity for the species-level detection (Ion AmpliSeq Microbiome Health Research Kit: www.thermofisher.com/ngsmicrobiome) of these bacteria and is hence better suited for gut microbiome profiling in the context of the above phenotypes, as compared to other existing solutions.

Methods To assess the utility of the panel in cancer immunotherapy research, we sequenced DNA from 15 stool samples from subjects with Non-Small Cell Lung Carcinoma (NSCLC) undergoing immunotherapy, and compared their microbiome profiles to 26 healthy stool samples collected internally. With our post-sequencing workflow on Ion Reporter™, we automatically generate a report with taxonomic classifications, sample diversity metrics through QIIME2 integration, and relative abundance visualizations for bacteria across multiple samples.

Results We identified significant microbiome composition differences between the healthy samples and cancer-treated samples, as evidenced by (i) a clear separation between the two cohorts based on a beta diversity principal coordinate analysis (PCoA) plot, driven by large abundance changes in Clostridium, Lachnoclostridium, Subdoligranulum and Oscillibacter (P < 0.05), (ii) grouping into distinct classes based on overall microbiome profiles (Analysis-of-Similarities ANOSIM P = 0.003), and (iii) differences in abundances of specific bacteria with anti-tumor effects such as F. prausnitzii (P = 0.02).

Conclusions We have created a highly multiplexed, sensitive and specific assay for robust characterization of gut microbiota, with compatibility on both (i) the Ion GenStudio S5™ with a 48-hr sample-to-result turnaround, and (ii) the new Ion Genexus™ System, a fully integrated platform featuring a hands-off, automated sample-to-report workflow that delivers results in a single day. It enables an efficient and affordable means for conducting extensive analyses of the human microbiome having applications in the study of phenotypic variability, and the potential relationship to disease. For research use only. Not for use in diagnostic procedures.

REFERENCE

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681 SINGLE PIPELINE RE-ANALYSIS REVISES MICROBIOME ASSOCIATIONS WITH ANTI-TUMOR RESPONSE TO CHECKPOINT INHIBITORS

1Fyza Shaikh*, 2James White, 3Joell Gilis, 4Taiki Hakozaki, 5Richard Corentin, 6Bertrand Routy, 7Yuusuke Okuma, 8Mykhaylo Usyk, 9Abbhishek Pandey, 10Jeffrey Weber, 11Jiyoung Ahn, 12Junadhika Naidoo, 13Evan Lipson, 14Drew Pollard, 15Cynthia Sears. 1Johns Hopkins School of Medicine, Baltimore, MD, USA; 2Resphera Biosciences, Baltimore, MD, USA; 3Tokyo Metropolitan Cancer and ID Center, Tokyo, Japan; 4University of Montreal Research Center, Montreal, Canada; 5Tokyo Metropolitan Cancer and ID Center, Tokyo, Japan; 6NYU School of Medicine, New York, NY, USA

Background Several studies suggest the gut microbiome may be a novel, modifiable biomarker for clinical efficacy of immune checkpoint inhibitors (ICIs). Microbiome profiling of pre-treatment samples demonstrated that high alpha-diversity and enrichment of specific bacterial species are associated with improved tumor responses in melanoma, renal cell cancer (RCC), and non-small cell lung cancer (NSCLC). Despite these reports, the specific bacteria or communities helpful or harmful have been inconsistent across study populations, and further correlation with immune and mutational biomarkers are limited or lacking. We hypothesize that, by use of a larger sample size and a consistent computational approach, we would derive a clearer microbial profile that correlated with immunotherapeutic outcomes.

Methods We re-analyzed the available raw 16S rRNA ampli-con and metagenomic sequencing data across five recently published ICI studies (n=303 unique patients) of responder (R) and nonresponse (NR) using a consistent computational approaches (Resphera Insight and MetaPhlAn2). Using novel microbiota signatures, we identified Re-analysis Indices for R- and NR-associated bacteria and validated the result in three addition cohorts with available raw sequencing data in patients with melanoma, hepatocellular cancer (HCC), and NSCLC (n = 105).

Results Our results confirm signals reported in each study, though some bacteria reported initially were not statistically significant after correction for false discovery rate. Likely, in part, because our analysis allows for comparison of individual species across cohorts, we were able to identify new bacterial signatures, such as Oxalobacter formigenes, Roseburia hominis and Veillonella parvula, Clostridium hathewayi, enriched in R and NR respectively. When our Re-analysis Index was compared to an index assembled from the literature, we noted improvement occurred in a sensitivity and specificity analysis, especially in NR-associated signals. Moreover, we found that alpha-diversity was not consistently predictive of response or nonresponse to ICIs. Our Re-analysis Index also validated in melanoma patients and HCC but did not perform as well in the NSCLC cohort, suggesting the need for further refinement based on tumor type.

Conclusions In summary, this bioinformatics platform improves on existing pipelines by standardizing critical preprocessing and downstream analysis tools, enabling comprehensive evaluations of taxonomic and functional signals across sequencing datasets. Notably, the NR-associated Re-analysis Index shows the strongest and most consistent signal using a random effects model and in a sensitivity and specificity analysis (p < 0.01). Our integrated analyses suggest an approach to identify patients who would benefit from microbiome-based interventions targeted to improve response rates by using a biomarker for nonresponse.

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Novel single-agent immunotherapies

682 ANTIBODY-MEDIATED BLOCKADE OF INTERLEUKIN-10 RECEPTOR-ALPHA PROMOTES THE ACTIVATION OF IMMUNE CELLS FROM IN VITRO DISASSOCIATED TUMOR SAMPLES


Background Interleukin-10 (IL-10) is a multifunctional cytokine that can mediate immune suppression or activation depending on the immunological context. Mouse studies have demonstrated that blockade of IL-10 enhances immune response against tumors and chronic viral infections,1 2 intriguingly,