INVESTIGATING THE EFFECT OF PROBIOTICS ON THE GUT MICROBIOME AND ON THE OUTCOME OF FOLFOX CHEMOTHERAPY IN COLORECTAL CANCER PATIENTS

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Introduction

Colorectal cancer (CRC) is the 5th most diagnosed cancer in Sub-Saharan Africa (SSA). In Kenya, CRC incidence rates have tripled from 1997-2017, with a rising incidence of early-onset CRC. Suggested pathobiology for this increase in CRC rates is gut microbiome dysbiosis. Moreover, FOLFOX chemotherapy for metastatic CRC is associated with gastrointestinal toxicity, and it also alters the patient's gut microbiome. Saccharomyces boulardii (S. boulardii), a probiotic with anti-inflammatory and anti-neoplastic effects, is a potential treatment for 5-FU induced-intestinal mucositis, chemotherapy - induced diarrhea. Given an increasing CRC incidence rate, the unknown local generalizability of CRC/microbiome research, and the high burden of chemotherapy - related morbidity, there is an unmet need to better understand how these factors influence CRC epidemiology in Kenya.

Aim of the work

1. To provide an overview of the microbiota composition differentiating CRC patients' gut profiles from healthy individuals' gut profiles.
2. To demonstrate the effect of probiotic supplementation on the outcome of FOLFOX chemotherapy in CRC patients.
3. To demonstrate the effect of probiotic supplementation on dysbiosis in CRC patients.

Subjects and Methods

In this single - center study conducted at Moi Teaching and Referral Hospital (MTRH), the mucosa-associated microbiome of 18 CRC patients and 18 healthy controls were identified by 16S rRNA sequencing and analyzed for diversity and biomarkers by alpha and beta diversity methods. Then, CRC patients were randomly assigned to receive FOLFOX or FOLFOX and S. boulardii probiotic. The primary end-point was to establish the tumor microbiome profile of Kenyan CRC patients relative to the healthy population and examine the probiotic consequences of S. boulardii upon chemotherapy.

Results

Of 18 patients enrolled, 7 received FOLFOX only, and 5 received FOLFOX and S. boulardii probiotic. Other six patients either discontinued the therapy or lost follow-up. Both study arms reported similar adverse events. However, diarrhea was worse in the probiotic group and couldn't be continued for more than four weeks due to severe diarrhea.

Microbiome analysis shows that alpha diversity analysis has no statistically significant quantitative species-diversity differences between healthy control and CRC groups for observed species (pObserved = 0.22). Beta diversity showed significant dissimilarities in the microbial communities between CRC patients and healthy controls (weighted UniFrac; stress = 0.1, p=0.04, unweighted UniFrac; stress = 0.181, p=0.0006). The most significantly overrepresented species in healthy samples compared to CRC samples were Prevotella copri, and Faecali bacterium prausnitzii. In contrast, for the CRC samples, we found that Bacteroides fragilis, Prevotella nigrescens, and Veillonella dispar were significantly overrepresented (LDA score > 2, $p<0.05$). F. prausnitzii, an anti-inflammatory microbiota associated with normal gut-barrier function, was depleted in CRC patients.

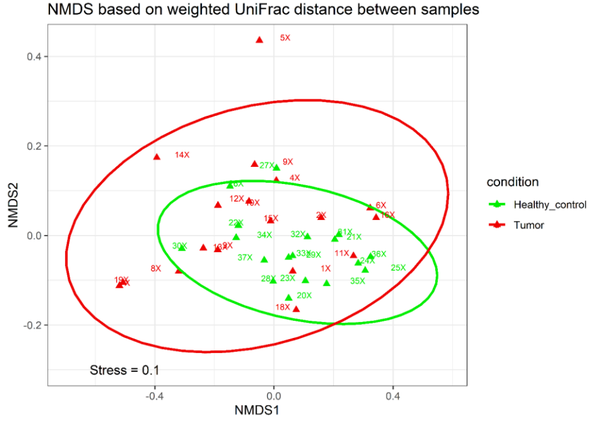

Figure 1: Beta diversity analysis: using a rank-based approaches, NMDS (Non-metric multidimensional scaling) with Unifrac dissimilarity. Points of red colors or shapes represent CRC samples; green colors or shapes represent samples of control. The closer the two sample points are, the more similar the composition of the two sample species is. The horizontal and vertical coordinates represent relative distances and have no practical significance. It is generally considered that stress <0.2 can be expressed by the two-dimensional dot pattern of NMDS, and its graph has a certain explanatory meaning.

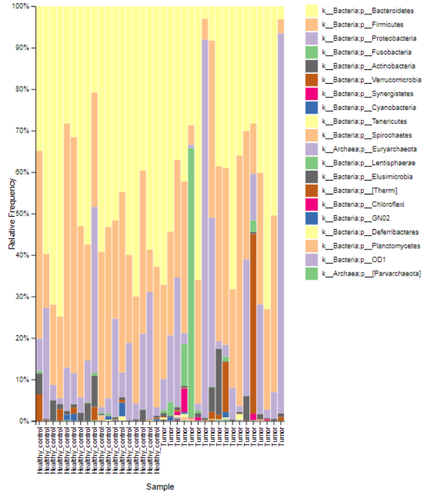

Figure 2: Taxonomic abundances across the samples (CRC vs. Healthy) CRC vs. Healthy

Conclusion

- There were significant differences between CRC microbiome compared to healthy individuals. CRC microbiome dysbiosis, particularly P. copri, and F. prausnitzii depletion, maybe a kind of signature of Kenyan CRC patients, and further studies may be of clinical interest. However, our results suggest S. boulardii as a treatment for chemotherapy-induced diarrhea is not advisable during FOLFOX therapy.