**ABSTRACT**

Colorectal cancer (CRC) poses a global health challenge as the third most diagnosed and second deadliest cancer worldwide. Current research suggests a pivotal role of the gut microbiome, an ecological community of commensal, symbiotic, and pathogenic microorganisms, in influencing CRC risk due to its integral role in maintaining host physiology and immune function. Despite mounting evidence connecting microbiome dysbiosis with CRC, the precise role of specific gut bacteria and their metabolites in CRC progression remains poorly understood. While vast quantities of metagenomic and metabolomic data have been generated to understand the CRC-associated microbiome, there remains a critical gap in establishing the functional roles of specific microbes and their small molecule metabolites within this disease context. The gut microbiota produces a myriad of metabolites; however, current methods fail to correlate these molecules directly to their microbial producers and subsequently, to CRC pathology and protection. This proposal centers on the hypothesis that a population of keystone gut bacteria and their metabolites significantly influence CRC oncogenesis or protective mechanisms. We posit that that these keystone bacteria and metabolites can be leveraged for preventive and therapeutic efforts. To test this hypothesis, we will conduct comprehensive analysis of fecal samples from CRC patients, adenoma (pre-CRC) cases, and healthy individuals, utilizing metabolomics and metagenomic approaches. By integrating these data with multi-omics and machine learning methods, we aim to identify and correlate specific bacteria to their pro- or anti-carcinogenic metabolites associated with CRC. Our preliminary data, encompassing 16S rRNA gene sequencing and untargeted metabolomics, have differentiated the microbiome and metabolite profiles among individuals with various stages of CRC and healthy controls, substantiating our research approach. We anticipate constructing a model that predicts the importance of specific bacterial populations and associated metabolites across disease stages. Furthermore, bioactivity-guided isolation and characterization of these metabolites via cell proliferation, immune response, and selective bacterial growth inhibition assays will be employed to evaluate their therapeutic potential. The findings could augment CRC risk assessment and inform microbiome-centered diagnostic and therapeutic intervention. The project innovates by combining high-throughput omics technologies with bioinformatics to reveal the microbiome’s chemical drivers’ role in CRC. This project aims to reduce the knowledge gap in microbial contributions to CRC by functionally linking microbial populations to their metabolic outputs, offering potential for novel diagnostic and therapeutic strategies. By elucidating these relationships, we may advance beyond association studies towards understanding the causative microbiome functions in CRC. Collectively, the successful execution of the proposed work could yield candidate bacteria and metabolites with defined roles in CRC prevention and treatment, and describe the therapeutic potential of gut-derived metabolites in CRC treatment.