Title: Impact of Obesity on Intestinal Tumorigenesis - Searching for Answers in the Microbiome, Metabolome and Transcriptome: Studies by the HNRCA Cancer Research Cluster and Tufts Computational Biology Initiative

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Abstract:

The HNRCA Cancer Cluster is a collaborative group of 20+ basic, epidemiological and clinical researchers drawn from several laboratories at the HNRCA, with the shared goal of conducting large research studies in emerging areas of nutrition and cancer.

There is general agreement that the risk of developing several of the most common cancers is determined in part by habitual dietary practices, which include total caloric intake, alcohol consumption, dietary macronutrients such as saturated fat, and minor components such as micronutrients and phytochemicals. The prototype of a nutritionally-determined cancer is colorectal cancer (CRC), where up to 30-50% of the attributable risk is attributable to dietary factors. There are approximately 150,000 new cases and 50,000 deaths from CRC every year in the US.

In order to design effective public health strategies to reduce the burden of CRC, dietary determinants of risk must be clearly defined and their mechanisms of action characterized. A role for the microbiome in health has long been postulated, however advances in sequencing have seen an acceleration in microbiome research over the last several years. The gut microbiome, consisting of 100 trillion cells (100x the number of cells in our body), has the potential to affect tumorigenesis by altering epithelial proliferation and differentiation, production of essential nutrients and/or bioactive food components, prevention of the overgrowth of pathogenic organisms and the stimulation of mucosal immunity, inflammation and innate defense. Importantly the composition of the gut microbiome is sensitive to diet and may also be impacted by host physiology.

We sought to compare the impact of high fat diet-induced and genetic-induced obesity on intestinal tumorigenesis using mice and, in collaboration with our partners in the Phoenix Lab, The TUCF Genomics Team, and the Computational Biology Initiative (CBI), conducted analyses of the gut microbiome composition, stool metabolome and mucosal transcriptome.

We observed that genetically-driven obesity induces a larger weight gain and tumor burden than high fat feeding, but relatively less changes in the microbiome. Tumor status was only associated with minor changes in the microbiome. Efforts to assimilate these observations with metabolomics and RNA-seq data are underway.