Dietary regulation of cancer immunity

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Abstract: Obesity is a worldwide epidemic that correlates with increased cancer incidence and immune dysfunction in several tissues such as intestine. There are life style factors that contribute to risk of obesity and cancer including pro-obesity diets such as high fat diets. While diet is considered as a preventable risk factor for many cancers, little is known about the causal mechanisms through which pro-obesity diets affect tumorigenesis and immunity. Our preliminary data suggest that a high fat diet leads to increased tumorigenicity in the intestine through several orthogonal mechanisms involving tumor initiating stem cells, immune cells and microbiome. However, how intestinal adaptation to diverse pro-obesity diets alters the interactions between these cellular networks and contributes to risk of cancer are still elusive. Moreover, it is important to assess the kinetics of altered cellular networks that contribute to intestinal cancer risk in the context of obesity or high fat diet. Here, we will comprehensively determine the precise mechanisms of diet-induced dampening of immunity by interrogating the interactions between epithelial cells, immune cells and microbes over time across different high fat diets. We will perform gene expression, metagenomics and metabolomics analyses and integrate these to discover multidimensional features and define potential causal mediators. Finally, we will determine how diverse diets modify intestinal carcinogenesis longitudinally. This will serve as a functional benchmarking study and a database that would inform further mechanistic studies. Ultimately, this project will provide comprehensive assessment of cellular and molecular features contributing to cancer risk in response to diet and obesity.