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Abstract:
Transformation of the gastric epithelium occurs in the setting of Helicobacter infection and chronic inflammation, and is mediated in part by epigenetic changes, but the role of nerves has not been studied. Preliminary data from our group has revealed that denervation of the stomach by truncal vagotomy markedly inhibits cancer of the gastric corpus in the INS-GAS mouse model. However, in contrast to the proximal INS-GAS tumors, classical intestinal-type gastric cancer in humans is largely a distal gastric neoplasm. Hence, we have phenocopied antral gastric cancer using a protocol (H. felis infection + MNU) that induces epigenetic alterations. In addition, we have shown that doublecortin-like kinase 1 (Dclk1) marks tuft cells, some long-lived that contribute to the niche, and also progenitor cells for the enteric nervous system (ENS). Our hypothesis, then, is that a close interaction between neural innervation and epigenetic modulation is necessary for initiation of gastric carcinogenesis. We propose three specific aims. (1). Can surgical or chemical denervation of the stomach inhibit antral gastric carcinogenesis? We will study the effects of vagotomy and chemical denervation in the H. felis/MNU model of antral gastric carcinogenesis using both prevention and treatment strategies. Moreover, we will examine the effects of truncal vagotomy on selected biomarkers in an ongoing phase I study of gastrectomy in human patients with gastric cancer. (2). What is the role of Dclk1+ progenitors in antral gastric carcinogenesis? Using Dclk1-CreERT mice, we will perform Dclk1 lineage tracing in mouse models of antral cancer. A diptheria toxin (conditional DTR/DT) strategy of cell ablation will be used to study the role of the Dclk1 tuft cells in antral gastric cancer. (3). What is the relationship between epigenetic modulation, neurogenesis, and genetic alterations in gastric cancer? We will use epigenetic modifiers (decitabine +/- gastrin) to study the impact on neurogenesis in the MNU/H. felis/GAS-KO model of gastric cancer. We will also examine the effects of denervation on epigenetic modulation. Finally, we will carry out exomic sequencing of tumors with and without vagotomy to determine the effects of denervation on carcinogen-dependent genetic alterations.
