Studying Gastric Cancer Pathogenesis using Correlative High-Resolution Microscopy and Genomics

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Although gastric cancer continues to be a global health issue, the management of gastric cancer remains limited. Novel therapeutic approaches to address this increasingly large unmet need necessitate the discovery of molecular targets that regulate each step in the gastric cancer (GC) cascade, which also represents an opportunity to identify biomarkers for early detection and treatment. Claudin (cldn)18 is the most highly expressed tight junction protein in human stomach, is down-regulated (no expression) in more than 80% of GCs with an intestinal phenotype, is down-regulated early in GC progression, and its attenuation is related to poor survival in advanced GC patients. Because little is known about cldn18, we aim to ascertain how the structural and molecular profile of gastric epithelial cells is affected by the attenuation of cldn18. For this, equipment in the Harvard Center for Biological Imaging (HCBI) will be used to determine, in a mouse GC model, the three-dimensional high resolution pattern of cldn18 expression in stomach from archived paraffin sections. Additionally, archived tissues from control and cldn18 knockout mice will be subjected to laser capture techniques and used to elucidate transcriptional dynamics and gene interactions that are correlated to cldn18. Strong preliminary data from an experienced team support the feasibility of this project on instruments in the HCBI that are not available otherwise. These studies should reveal important insights into the role of cldn18 in GC pathogenesis that can be translated to early biomarker analysis in human disease.