Esophageal cancer patients suffer one of the poorest survival rates (14%) of all cancer types. Esophageal squamous cell carcinoma (ESCC) and the now predominant esophageal adenocarcinoma (EAC) differ dramatically in their cell of origin deriving from either squamous or intestinal metaplasia associated lineages respectively. This transition to the intestinal metaplasia known as Barrett's esophagus (BE) parallels the differentiation pathways of the lower intestine but carries an increased life time risk of dysplasia and is commonly observed in those presenting with EAC. Underlying the development of both BE and EAC is a history of gastro-esophageal reflux disease (GERD) leading to inflammation and ulceration that, when combined with as yet ill-defined genetic propensities, is proposed to alter the reparative or regenerating esophageal epithelium towards this metaplastic intestine-like lineage. However, anatomical differences between humans and model organisms have hampered supportive direct evidence. In this seminar I will discuss and demonstrate the routes through which GERD, inflammation, intestinal metaplasia and somatic variation contribute to the development of EAC through genomic and functional studies of the intestinal-like nature of BE, single cell sequencing of stem cell derived “mini gut” or organoids of BE, functional genomic screening of EAC cells and cancer genome atlas data of esophageal cancers. Collectively these studies suggest the possibility of a GERD driven positive selection of intestine-like cellular lineages and clonal cell populations with GATA factor amplifications during both BE and EAC development with implications for patient outcome and treatment.