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Single-cell analysis of multiple cancers in the upper gastrointestinal tract uncovers immune characteristics of tumor microenvironments linked to the predictive biomarkers for immunotherapy

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Esophageal cancer is mainly composed of two subtypes – esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) – each with distinct risk factors and cancer phenotypes despite arising from the same organ. The recent study by the Cancer Genome Atlas (TCGA) has revealed their distinct genomic characteristics and similarities to other nearby cancers such as head and neck squamous neck carcinoma (HNSCC) and gastric adenocarcinoma (GAC) for ESCC and EAC, respectively. Furthermore, recent clinical trials with anti-PD-1 monotherapy and combination treatment with anti-CTLA-4 reported varying degrees of responses to immunotherapy among those cancers. Here we performed single-cell RNA sequencing of patients with ESCC, EAC, and HNSCC, and collected additional public datasets for comparative analysis of four cancer types in the upper gastrointestinal tract, especially in connection to responses to immunotherapy. In total, we integrated 35 patient samples from 4 different cohorts to comprehensively analyze malignant cells, stromal/endothelial cells, and immune cells. With the integrative analysis, we systematically compared the similarities and differences among those cancer types and expanded understanding of immune mechanisms at single-cell resolution. For malignant cells, we utilized matrix factorization analysis to identify underlying malignant cell programs related to each cancer type. We confirmed clear separation between malignant cells of squamous epithelial cell origins and glandular epithelial cell origins. We further identified the malignant cell programs related to both cancer cell origins and molecular mechanisms of cancer cells. For immune cells, we identified their underlying immune mechanisms that could explain key differences in responses to immunotherapy. With comprehensive analysis of various immune cell-types and their interactions, we identified several T cell populations and related tumor-associated macrophages that could serve as predictive markers of responses to immunotherapy. To validate our findings, we utilized both bulk and single-cell sequencing datasets of various cancer types with treatments of immune checkpoint inhibitors (ICI) and confirmed significance of those immune signatures and cellular compositions in predicting ICI responses.

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