Dissecting tumor cell state heterogeneity in advanced prostate cancer

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Background: Metastatic castration resistant prostate cancer (mCRPC) is a lethal disease that invariably develops resistance to therapies targeting androgen signaling. Significant phenotypic and transcriptional heterogeneity has been observed in mCRPC tumors, including the emergence of AR-negative and neuroendocrine (NE)/small cell histologies, that likely represent adaptive mechanisms of resistance and are difficult to target therapeutically. Clinically, therapeutic responses can also vary both between patients and among metastatic sites within the same patient, yet the mechanisms that drive differential tumor response and behavior remain poorly defined. As such, understanding how distinct tumor cell states evolve in mCRPC and the molecular drivers that sustain them are key to developing new targeted therapy approaches. Here we profile metastatic prostate tumors from a wide array of metastatic organ sites using multiomic single cell approaches, to dissect mechanisms of transcriptional dysregulation in advanced disease.

Methods: To directly examine tumor cell state heterogeneity in mCRPC, we used single nuclei RNA-sequencing (snRNA-seq) to profile 36 metastatic tumors across 21 patients, sampling diverse metastatic organ sites, including liver, lung, bone, and lymph node. Several of these were obtained as part of a rapid autopsy program and sample distinct metastatic tumors from the same patient, enabling direct comparisons between metastatic niches. We have additionally profiled a subset of these samples using combined single cell RNA- and ATAC-sequencing to capture chromatin accessibility, which will allow investigation of the regulatory underpinnings driving transcriptional phenotypes.

Results: In comparing tumor cell transcriptional states across patients and metastatic organ sites, we observe a proliferative tumor cell population that appears to be shared between different metastatic lesions. In addition to shared tumor cell states, we also find heterogeneity between different tumors even within the same patient, including differential enrichment of AR-driven and neuroendocrine transcriptional signatures. We are currently working to extend our analyses across our entire dataset to characterize the cellular make-up and lineage of each metastatic lesion, and to understand how distinct cell states evolve and develop. We anticipate reporting additional results from these studies at the meeting.

Conclusions: We observe tumor cell heterogeneity across mCRPC tumors and metastatic organ sites that highlights the challenge of treating this disease. Our future studies aim to better characterize the underlying biological drivers to identify more effective therapeutic targets.

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