

Organ-specific fitness shapes lineage plasticity in metastatic prostate cancer

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Background: Despite advances in the treatment of metastatic prostate cancer, the disease course is almost invariably marked by evolution toward a therapy-resistant and lethal phenotype. Concurrent alterations in PTEN, TP53, and RB1 are enriched in advanced disease and are associated with androgen receptor (AR)-independent lineage plasticity and neuroendocrine differentiation. However, whether resistance develops through the same cell states at different metastatic sites remains poorly understood. In this study, we used PDM136, a patient-derived multi-organ metastasis model that harbors TP53, PTEN, and RB1 alterations and develops AR-positive metastases, to define tumor cell states in bone, liver, and adrenal metastases before and after castration.

Methods: Luciferase-labeled LuCaP136 cells were inoculated into the left cardiac ventricle of male NSG mice to generate multi-organ metastases. To capture dynamic cellular evolution, we performed longitudinal single-cell RNA-seq (scRNA-seq) on tumor cells across intact, early, intermediate, and late castration stages from bone, liver, and adrenal metastases. scRNA-seq of these samples plus two subcutaneous parental tumors yielded gene-expression profiles from 99,376 tumor cells after quality control. Computational analyses were used to identify 12 major cell states and recurrent gene-expression programs. Histology and immunohistochemistry for AR, ASCL1, synaptophysin, and SOX2 were used to confirm these phenotypes in tissue.

Results: Before castration, most tumor cells at all three metastatic sites expressed AR, but their cellular composition differed by organ. Bone metastases were the least heterogeneous, adrenal metastases showed intermediate heterogeneity, and liver metastases were the most diverse. Liver metastases also contained pre-existing populations with neuroendocrine features, suggesting earlier neuroendocrine differentiation at this site. Following castration, AR-dependent populations decreased and AR-independent populations expanded in every organ. However, the resistant states that came to dominate were organ-specific. Liver metastases became strongly enriched for AR-negative neuroendocrine cells, whereas bone metastases preferentially expanded with double-negative features. Adrenal metastases developed a mixture of these resistant states. Neuroendocrine cells showed gene-expression programs associated with inflammatory and growth-factor signaling, proliferation, and changes in cell identity. Double-negative cells instead showed programs associated with low-oxygen stress, altered glucose metabolism, and cellular plasticity. These programs also differed by site, with neuroendocrine programs most prominent in liver and adrenal metastases, low-oxygen programs most prominent in liver, and a more epithelial program retained in bone.

Conclusions: Our results indicate that castration drives metastatic prostate cancer toward AR independence, but not through a single evolutionary path. Instead, bone, liver, and adrenal metastases favor the survival and expansion of distinct resistant cell states. These findings suggest that organ-specific fitness contributes to lineage plasticity and may inform therapeutic strategies directed at both tumor cell state and metastatic site.

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