Investigating the heterogeneity of circulating tumor cells in a mouse model of metastatic prostate cancer

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Background: Tumor heterogeneity in prostate cancer is thought to be associated with the phenotypic and genetic diversity of tumor cells and is considered a crucial intrinsic driver of cancer progression and metastasis. However, the mechanisms underlying cell heterogeneity are unresolved in part due to inherent challenges in accessing and evaluating metastatic samples from patients. Furthermore, while circulating tumor cells (CTCs) are a valuable resource for studying the cellular diversity, they are particularly difficult to access and thereby it is challenging to study their molecular and phenotypic properties. **Methods**: To achieve this, I have developed approaches for isolation and enrichment of CTCs from a genetically engineered mouse model (GEMM) of metastatic prostate cancer. Key features of this GEMM include its complete penetrance of metastasis, and that it incorporates a lineage marking reporter to track tumor cells during disease progression and dissemination. To study tumor heterogeneity during dissemination, I have established new methods to generate organoids from single CTCs. **Results**: Having established single cell-derived organoid cultures from CTCs, I have applied single-cell sequencing based technologies to dissect their molecular features. We have found that single cell CTC-derived organoids have molecular diversity and cluster into distinct subpopulations. Ongoing analysis are aimed at understanding the landscape of cellular heterogeneity present in CTC derived organoids with the goal of elucidating mechanisms of tumor dissemination and metastatic progression.

Conclusions: CTC- derived organoids generated from a GEMM of prostate cancer metastasis show intra-heterogeneity associated with different molecular profiles, which can be further investigated to uncover candidate alterations associated with metastatic dissemination. Thus, the goal is to link this diversity to the molecular alterations associated with metastatic potential in CTCs.

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