Reanalyzing transcriptomic profile of castration-resistant prostate cancer

YUANHONG ZENG[1,2], Tian He[2], Chia-Chun Chen[2], Wendy Tran[3], Thomas G. Graeber[1,4,5,6,7]

1 BIG Summer Program, Institute for Quantitative and Computational Biosciences, UCLA
2 Department of Molecular and Medical Pharmacology, University of California Los Angeles (UCLA), Los Angeles, CA, USA
3 Department of Microbiology, Immunology, and Molecular Genetics, UCLA, Los Angeles, CA, USA
4 Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, USA
5 Crump Institute for Molecular Imaging, UCLA, Los Angeles, USA
6 California NanoSystems Institute, UCLA, Los Angeles, USA
7 Metabolomics Center, UCLA, Los Angeles, USA

Abstract

Castration-resistant prostate cancer (CRPC) often progresses to more aggressive forms that develop resistance to androgen receptor (AR) targeted therapy, including small cell neuroendocrine prostate cancer. Several recent studies have developed preclinical models to understand cancer progression dynamics. Here, we utilized the Toil pipeline to reprocess the RNA-seq data from a xenograft model that recapitulates therapy induced lineage plasticity during CRPC progression. Furthermore, we compared this data to other datasets and experimental models, mainly by looking into differentially expressed genes and altered key pathways, as well as by performing principal component analysis (PCA) projections. The goal is to generate a comprehensive analysis on transcriptome profiling across various datasets and preclinical models that will potentially contribute to future research discoveries.

Introduction

In reponse to androgen deprivation therapy, tumours can escape epithelial lineage confinement and transition to a high-plasticity state. This change in phenotype often means more aggressive tumor and low survival rate. Recent researches build xenograft models to understand the mechanism

Davies et al. generated a ENZ (enzalutamide) driven resistant model

Tang et al. identifies 4 subtypes by clustering on ATAC-seq assay of patient derived organoid, xenograft, and cell lines

Sample type	Description
LNCaP	Cell line of metastatic prostate carcinoma, expresses AR
16D	Xenograft of castration-resistant prostate cancer
49F	Xenograft of ENZ resistant prostate cancer, expresses AR, and with high AR pathway activity
42D	Xenograft of ENZ resistant prostate cancer, expresses AR, and with low AR pathway activity
42F	Xenograft of ENZ resistant prostate cancer, expresses AR, and with low AR pathway activity

Sample type	Description
Group AR	AR-dependent subtype, rely on androgen receptor pathway signaling
Group WNT	Subtype with high Wnt signaling pathway activity
Group NEPC	Subtype that exhibit characteristic of neuroendocrine cell, AR independent for growth
Group SCL	Subtype that exhibit stem cell like phenotype, driven by AP-1 family of transcription factor

Table 1: description of samples from Davies et al (left) and Tang et al (right) dataset

Method

We use Toil pipeline to reprocess the RNA-seq datasets from the literatures. With this, we are able to reduces computational batch effect and perform cross-dataset analysis. We processed the datasets following the workflow. We generate alignment using STAR and perform quantification using RSEM.

Dataset	# samples	type of samples	Description
Tang et al 2022	35	Organoids, xenograft, and cell lines	22 patient-derived organoids, 6 patient-derived xenografts (PDXs), and 7 cell lines
Davies et al 2021	10	LNCaP derived Xenograft	Xenograft tumors that developed resistance under ENZ treatment
Beltran et al 2019	64	Clinical samples	CRPC and NEPC tumor
Abida et al 2019	85	Clinical samples	CRPC and NEPC tumor
Sharp et al 2019	41	Clinical samples	Metastasis CRPC tumor
Labrecque et al 2019	97	Clinical samples	Metastisis CRPC tumor

Table 2: Toil processed RNA-seq dataset

Results

Cross dataset projection reveals similar subtypes

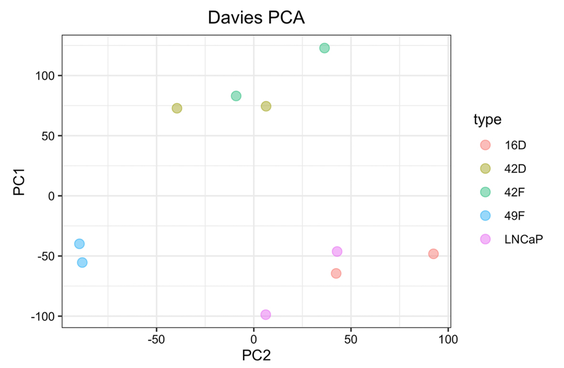

Fig 1: PCA of samples from the Davies et al dataset. Notable similarities observed between samples 42D and 42F, as well as 49F and LNCaP, as depicted by their close proximity in the plot.

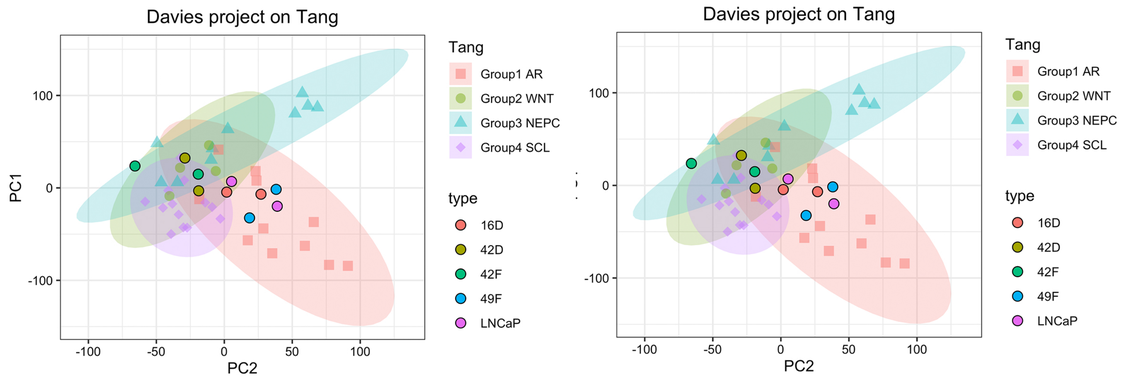

Fig 3: Davies samples projected onto the principal components of Beltran and Tang. Shaded ellipses represent a 0.95 confidence level under the assumption of normal distribution.

GSEA identifies key pathways associate with subtypes

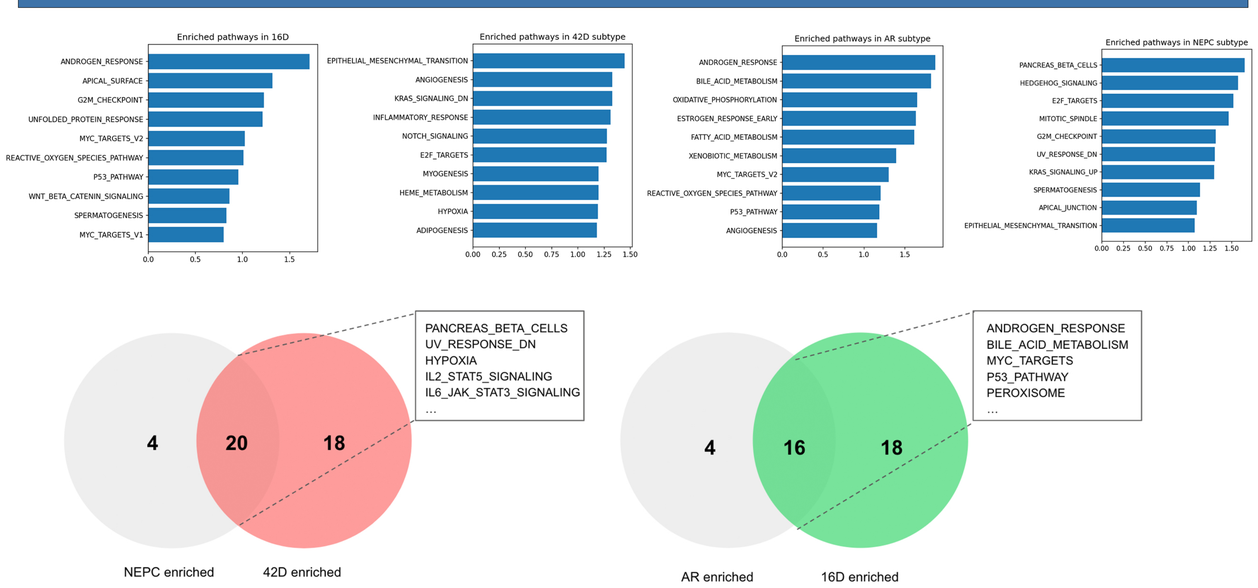

Fig 4: Pathways enriched across various subtypes, analyzed using a one-out comparison method within both the Davies and Tang datasets.

Fig 5: Shared pathways between the NEPC subtype and 42D, as well as the AR subtype and 16D. The figure highlights the top enriched pathways within these paired groups.

Key References

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