Identification of key transcription factor target interactions that regulate prostate cancer responses to Androgen Deprivation Therapy and Metastasis


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Background: The standard of care for patients with aggressive prostate cancer is androgen deprivation therapy (ADT), but the benefits are often short-lived, and the transcriptional responses to ADT are not well understood.

Methods: We generated whole transcriptome gene expression data by Illumina sequencing of total RNA from 24 patient-matched formalin-fixed Pre-ADT prostate needle core biopsies and corresponding formalin-fixed Post-ADT radical prostatectomy samples. We used the PANDA algorithm to integrate RNAseq expression data, protein-protein interaction databases, and DNA binding motif data to reverse engineer transcriptional networks.

Results: Differential gene expression analysis revealed two subgroups of Post-ADT samples displaying strong or weak transcriptional responses to ADT. We observed that after ADT treatment, there was a selection towards a more aggressive, ADT-resistant, androgen receptor-independent subtype (PCS1) in the strong responders, and a less aggressive, basal-like subtype (PCS3) in the weak responders. We identified transcription factor coordinated groups (TFCGs) that shared over 70% of predicted target genes. We compared strong responders to metastatic networks by leveraging a large dataset (n > 1200) of multiple publicly available cohorts that were transcriptionally subtyped by You et al. More than 95% of the Key TFs in the metastatic network were a subset of the strong responder’s network Key TFs. We identified TFCGs enriched in both the strong responders and metastatic networks, suggesting putative common regulators related to differential responses to ADT and subsequent metastatic progression. We found 20 such TFCGs that included groups such as GLI3-GLI2 and HOXA10-SOX4-GATA4. Some TFCGs lost members and targeted a distinct set of genes in the metastases, possibly suggesting a concerted re-localization. Another TFCG (ERF-ETV5-ETV3-ELF4) gained HIF1A in the metastatic network. Finally, we observed coordination of AR with CEBP factors (AR-CEBPΔ-CEBPG-CEBPE) in both datasets.

Conclusions: Our unbiased method to identify transcription factor coordination using independent datasets has revealed important putative regulators associated with differential responses to ADT and metastatic progression.

Conflict of Interest: The authors no conflicts to declare.

Funding Acknowledgments: Funding for this work was provided by the Movember Foundation Global Action Plan (GAP1).