Mechanistic and functional interplay between epithelial plasticity and androgen receptor in driving enzalutamide resistance

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Background: In the US, metastatic prostate cancer is responsible for over 80 deaths per day. The overwhelming majority of these deaths are due to metastatic castration-resistant prostate cancer (mCRPC). Standard-of-care treatments for mCRPC are hormonal therapies that target the androgen receptor pathway, such as abiraterone acetate and enzalutamide; however, development of resistance to these drugs is inevitable. Therefore, it is imperative that we elucidate the molecular mechanisms of resistance to these therapies.
Methods: To identify mechanisms of enzalutamide resistance, our laboratory developed a series of enzalutamide-resistant cell lines by chronic exposure to increasing doses of enzalutamide and performed RNA-Seq and phospho-proteomics analysis.
Results: Consistent with previous investigations, we observed relatively few gene expression changes common to all cell line models (340/2,768 genes, 12% overlap). Conversely, phosphorylation events common to all lines were highly concordant (57/115 genes; 50% overlap). These data suggest that while the individual cell lines may have unique gene expression programs in response to enzalutamide, these gene expression programs converge on key signaling nodes at the protein level. We reasoned that these common signaling nodes could be identified by integrating the RNA-Seq and proteomics data in a pathway-based approach. Along these lines, gene set enrichment analysis of the RNA-Seq and proteomics data revealed common enrichment of epithelial-mesenchymal transition (EMT) in all three enzalutamide-resistant lines. To better understand the role of EMT in driving enzalutamide resistance, we induced EMT in enzalutamide-sensitive cells using the EMT master regulator, Snail. Remarkably, Snail-induced EMT induction led to enzalutamide resistance. Similarly, knockdown of Snail in enzalutamide-resistant cells re-sensitized cells to enzalutamide. We also noted a significant upregulation of full-length androgen receptor and the androgen receptor splice variant, AR-V7. Knockdown of either full length AR or AR-V7 in the context of Snail upregulation re-sensitized cells to enzalutamide. Together, these results suggest that Snail-induced EMT drives enzalutamide resistance, in part, through androgen receptor signaling.
Conclusions: Our integrative analysis of gene expression and proteomics data from enzalutamide-resistant cell line models pinpointed the EMT pathway as a potential target for therapy in enzalutamide-resistant mCRPC. Co-inhibition of EMT and AR together may prevent or delay resistance to AR-targeted therapies.

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