Convergent hormone therapy resistance mediated by stress/dormancy-like pathways in prostate cancer

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Background: Novel agents that inhibit the androgen receptor (AR), including abiraterone acetate and enzalutamide, have significantly prolonged life in many men with metastatic castration resistant prostate cancer (mCRPC). However, after 1-2 years of therapy acquired resistance to these drugs is nearly universal. Therefore, identifying mechanisms of resistance and innovative therapies to treat enzalutamide-resistant disease represents a major unmet clinical need.

Methods: In this study, we developed four enzalutamide resistant cell lines and analyzed each cell line by RNA-seq and phospho-proteomics to identify common pathways deregulated during disease progression to enzalutamide resistance. We manipulated p38α levels and activity in order to determine its mechanistic relationship to resistance. We measured p38α activity in metastatic biopsies from men with both hormone sensitive and metastatic prostate cancer.

Results: At the nexus of acquired enzalutamide resistance in four independently-derived prostate cancer model systems, we identified a convergent mechanism of resistance through activation of the p38α stress response/dormancy pathway. Enzalutamide resistant cells are sensitized to p38α inhibition, and enzalutamide sensitive cells developed resistance to enzalutamide with constitutive activation of p38α signaling. Enzalutamide resistant cells have sustained AR activity, which is blocked with genetic or small molecule p38α inhibition indicating p38α promotes AR activity in the absence of ligand binding. Finally, we found common activation of p38α in lymph node, visceral, and bone metastases from men with mCRPC.

Conclusions: We have identified the stress response/dormancy p38α-signaling pathway as a common mechanism driving enzalutamide resistance. Most importantly, p38α is a targetable pathway activated in tumors from men with mCRPC, suggesting novel therapeutic strategies could be applied to prolong the lives of men with metastatic, drug-resistant prostate cancer.

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