Identifying Novel Gene Deletions as Predicting Biomarkers of Antiandrogen Resistance in Advanced Prostate Cancer

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Background:

Patients with advanced prostate cancer (PCa) are frequently treated with antiandrogens such as enzalutamide. Unfortunately, nearly 60% of patients exhibit early resistance to antiandrogen, with most initial responders eventually becoming resistant to treatment. Given this, there is an urgent need to understand the mechanism of resistance and identify novel biomarkers for predicting antiandrogen response. The highly heterogeneous nature of advanced PCa strongly suggests that this genetic heterogeneity may be the main determinant of sensitivity and resistance to antiandrogen therapy.

Methods & Results:

Our previous work revealed that advanced prostate cancer with *TP53/RB1* alterations could acquire lineage plasticity and use it as a means to escape luminal-specific drug therapy targeting AR, through up-regulation of *SOX2*. However, patients carrying alterations in these two loci only account for less than half (40%) of patients who ultimately develop resistance. Therefore, additional genomic alterations must be responsible for resistance in these other CRPC tumors. To identify the genetic alterations that lead to antiandrogen resistance, we successfully conducted an *in vivo* shRNA-based library screen and identified several prime candidate genes which confer antiandrogen resistance when deleted or mutated. including *SYNCRIP* and *CHD1* as the top 2 candidates. Using both the CRISPR/Cas9 and shRNA system, I have generated LNCaP/AR prostate cancer model carrying knockdown or complete deletions of *SYNCRIP* and *CHD1* and demonstrated that both the shRNA-mediated knockdown and complete deletions of these two genes can confer significant enzalutamide resistance both *in vitro* and *in vivo*. We are now working on elucidating the molecular mechanisms of these resistance, in effort to develop novel therapies or biomarkers.

Conclusion:

The genetic heterogeneity in advanced PCa could be the major reason of various responses to antiandrogen resistance. Given that there are ~15% patients carrying *SYNCRIP* deletion and ~10% carrying *CHD1* deletion based on several PCa cohorts, the completion of this project will not only add clarity to the underlying mechanism of antiandrogen resistance but may also lead to the development of novel predicting biomarker, as well as combination therapy that would overcome resistance, consequently providing greater clinical benefit to patients with advanced PCa.

Conflict of Interest:

No

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