

Development of a rational triple combination therapy for castrate-resistant prostate cancer

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Background

The androgen receptor (AR) signaling pathway drives prostate cancer development and progression, making it a major target for drug development. However, resistance to AR targeted therapies invariably develops and eventually leads to an aggressive, castrate-resistant prostate cancer (CRPC). Although CRPC often remains dependent on AR signaling, anti-androgen therapies can lead to the development of AR independent disease and metastatic CRPC. Understanding the molecular basis of this transition and resistance to current anti-androgen therapy will provide important insight and reveal novel therapeutic strategies for both AR-positive and -negative disease pathways.

Methods and Results

We analyzed *in silico* data of AR (signaling)-positive or -negative human CRPC tissue samples and discovered that MET expression is specifically increased only in AR-negative CRPC samples. When AR-positive CRPC models are subjected to AR signaling inhibition (by the AR antagonist enzalutamide or androgen deprivation), MET is increased and susceptible to activation by its ligand HGF. Therefore, we postulate that dual targeting of AR and MET signaling pathways may be a better approach to prevent and overcome resistance-related disease progression. Our preliminary AR ChIP-seq data suggested that MET transcription is not affected by AR directly rather, MET protein is modulated by AR signaling at the post-translational level. Therefore, we hypothesize that a combination therapy of a proteasome inhibitor and MET inhibitor may have potential therapeutic benefit for some CRPC patients. By using *in vitro* and *in vivo* models of AR-dependent CRPC, we have showed that combination of the dual MET/VEGFR2 inhibitor cabozantinib and enzalutamide treatment is more efficacious than either inhibitor alone. In addition, Bortezomib, an FDA-approved proteasome inhibitor, showed significant synergistic effect when paired with cabozantinib in our preliminary data using *in vitro* and *in vivo* CRPC models. *In vitro* results suggest that triple combination of anti-androgen, MET inhibitor and proteasome inhibitor therapies will maximize inhibition in CRPC.

Conclusion

MET is a compensatory survival pathway in AR+ CRPC upon anti-androgen therapy. The rational for triple combination of anti-androgen, MET inhibitor and proteasome inhibitor therapies is a feasible approach to maximize inhibition in CRPC while minimizing development of drug resistance to any single agent.

Conflict of Interest Statement

No potential conflicts of interest were disclosed.

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