MCT inhibition as a potential therapeutic strategy to target enzalutamide-resistant prostate cancer

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Background: The majority of prostate cancer (PCa) patients treated with androgen deprivation therapy develop resistance to the therapy, thus generating a dire need for establishing newer targets and approaches for the management of therapy resistant PCa. Enzalutamide is a second generation antiandrogen used for the treatment of metastatic castration-resistant PCa. However, resistance to enzalutamide is a significant issue and the mechanisms involved and strategies to overcome the resistance are under intense investigation.

PCa energetic metabolism is unique. Primary PCa are not predominantly glycolytic with increased glycolysis being found only in advanced stages, indicating that PCa are more heterogeneous in their use of energy sources. However, accumulation of the metabolic end product lactate is toxic and cancer cells upregulate the expression of monocarboxylate transporters (MCTs) to facilitate lactate efflux. Different MCT isoforms are differentially expressed in PCa with an increase in the expression of MCT2 and MCT4 during progression from benign prostate to carcinoma and high MCT4 expression in invasive PCa. Based on preliminary data, we hypothesized that MCT inhibition may be an attractive therapeutic strategy against enzalutamide-resistant PCa cells.

Methods: We analyzed the expression levels of MCTs in PCa tissues using public datasets from Oncomine and the relative expression levels of MCTs in enzalutamide-resistant and parental PCa cells using qPCR. We treated enzalutamide-resistant and parental PCa cells with varying concentrations of MCT inhibitors AR-C155858, AZD3965, or syrosingopine either singly or in combination with enzalutamide and assessed cell survival, proliferation, clonogenic ability, and tumorigenicity.

Results: We found that the suppression of MCT activity using the MCT antagonists AR-C155858, AZD3965, or syrosingopine not only diminished the proliferation, survival, clonogenic ability, and tumorigenicity of PCa cells, but also resensitized resistant cells to treatment with enzalutamide. These findings imply that MCTs may have an intrinsic role in resistance to therapy, which can be disrupted using MCT inhibitors.

Conclusions: MCT inhibition may be an effective strategy to overcome enzalutamide resistance in PCa.