K-11706 exerts potent anti-cancer activity via suppression of GATA2/AR/cMyc signaling axis in castration resistant prostate cancer

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Background: Despite recent therapeutic advances, prostate adenocarcinoma (PC) progression to lethal castration-resistant PC (CRPC) remains a major clinical problem, creating an unmet need for innovative treatment approaches. Targeted therapies for PC have mostly focused on the androgen receptor (AR) axis, while several other PC drivers, such as GATA2, c-Myc, FOXM1, CENPF, and EZH2, remain undruggable in the clinic so far.

We and others have previously reported several critical functions of GATA2 in AR signaling in PC: GATA2 induces AR expression; serves as a pioneer factor for AR binding to chromatin; and also post-translationally promotes transcriptional activity of both full-length and splice-variant AR. GATA2 is often elevated in CRPC.

Methods: Here, we investigated the role of GATA2 in PC cells beyond the AR signaling axis, and characterized the pharmacological potency of the GATA2 small molecule inhibitor (SMI) K-11706 against PC cells.

Results: Chromatin immunoprecipitation and RNA sequencing analysis revealed that GATA2 is a key modulator of cMyc expression, which induces the expression of FOXM1 and EZH2. We extensively profiled five CRPC cell lines following treatment with K-11706, which inhibited the proliferation and invasive behavior of PC cells, and dramatically reduced the genome-wide transcriptional activity of GATA2, AR, and cMyc, leading to downregulation of several PC drivers and AR/cMyc effector genes, notably FOXM1, EZH2, and CENPF. Transcriptional profiling and functional pathway analysis of the K-11706 transcriptomic footprint against curated databases delineated a biological network composed of genes involved in cell cycle/proliferation, stemness, metastasis and DNA repair. In vivo, K-11706 suppressed the growth of multiple cell-derived and patient-derived xenograft PC models.

Conclusions: We propose that GATA2 is a master regulator of multiple PC drivers and a promising actionable therapeutic target in CRPC. Pharmacologic inhibition of GATA2, via a potent second-generation small molecule inhibitor is feasible and effective in PC models both in vitro and in vivo.

Conflict of Interest: None

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