Molecular drivers of metastatic castrate-resistant prostate cancer: New roads to resistance

Phoebe A. Huang, Douglas K. Price, and William D. Figg

Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

ABSTRACT
Numerous growth-inducing signaling pathways have been implicated in the development of metastatic castrate-resistant prostate cancer, but their cross-talk with androgen receptor functions remains poorly understood. A recent study published in *Science Signaling* by Chen et al. has identified a novel androgen-mediated signaling axis driven by loss of SPDEF and gain of TGFBI to facilitate metastasis, which may explain the acquisition of resistance to androgen deprivation therapy. These findings suggest that therapeutic inhibition of androgen signaling may inadvertently promote castrate resistance by inhibiting tumor suppressive functions of the androgen receptor.
SPDEF. This may explain why loss of SPDEF irreversibly promotes TGFBI-mediated progression of mCRPC, despite reactivation of AR signaling after prolonged ADT.2,4

While previous studies have characterized a plausible role of SPDEF in suppressing tumorigenesis and EMT progression,11 Chen et al. are the first to situate the transcription factor within an AR-SPDEF-TGFBI signaling axis. Assessment of clinical tissue samples revealed elevated TGFBI expression in high grade tumors, and reduced SPDEF expression in tumors from patients who had received ADT. Conversely, low TGFBI and high SPDEF expression correlated with improved survival. Although ADT initially reduces primary tumor growth, loss of tumor suppressive SPDEF following therapeutic AR inhibition may explain the eventual development of resistance. A more thorough understanding of SPDEF expression during prostate cancer progression, particularly in response to clinical treatment strategies, may aid predictive screening strategies to distinguish aggressive disease relative to SPDEF expression.9 The AR-SPDEF-TGFBI signaling axis may alternatively be exploited to devise new therapeutic targets, such as SPDEF delivery by gene therapy or TGFBI-directed antibody antagonism.12 Combinatorial treatment strategies targeting the AR-SPDEF-TGFBI pathway along with administration of ADT may be able to delay or even prevent EMT progression before the development of castrate-resistant disease.

Another possibility may be to assess SPDEF expression levels during intermittent androgen deprivation, a treatment strategy currently investigated for its potential benefits.13 Studies have indicated that alternating maximal androgen blockade with periods of treatment cessation can prolong treatment sensitivity and delay progression to mCRPC without compromising efficacy,3,13 and preliminary clinical data has suggested that systemic androgen depletion by ADT beyond a certain low threshold may actually promote the survival and adaptation of more aggressive tumors.3 Though the consequences of intermittent therapy remain controversial, monitoring SPDEF expression levels may help determine whether treatment cessation would allow SPDEF recovery and protect against its loss between treatment cycles. Enhanced understanding of SPDEF response to ADT has the potential to aid in predicting therapy resistance and preventing the development of non-curative ADT resistance.

The discovery by Chen et al. of a mechanism by which SPDEF regulates androgen-mediated inhibition of TGF-β signaling, which can initiate EMT and bone metastasis in prostate cancer, sheds light on the role of AR in response to ADT-mediated selection pressures. Whether targeting the AR-SPDEF-TGFBI signaling axis can effectively prevent or counteract progression to mCRPC remains to be seen. These findings may fill a crucial gap in knowledge regarding acquired resistance to ADT by multiple mechanisms, particularly those that promote alternative signaling pathways. Resistance to ADT represents a major challenge for patients with recurrent disease, and continued efforts to assess the long-term consequences of androgen deprivation are clinically imperative. Identifying the principal mechanisms underlying this resistance is of critical importance to overcome barriers to prostate cancer treatment.

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