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

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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.[1] 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.

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Androgen deprivation therapy (ADT) remains the standard treatment paradigm for patients with locally advanced and metastatic prostate cancer.[2] Treatment is initiated using pharmacological inhibitors of the androgen receptor (AR), a key transcription factor involved in prostate growth and differentiation.[2,3] Although AR signaling inhibition is initially clinically effective, all patients inevitably show disease recurrence,[2,4] indicating progression to metastatic castrate-resistant prostate cancer (mCRPC). A variety of mechanisms underlying the acquisition of resistance have been implicated since the discovery of genetic aberrations resulting in AR signaling modulation and reactivation.[2] However, the overall rates of AR gene amplifications and increased AR protein expression only account for a subgroup of mCRPC cases,[5,6] and the complexity of AR cross-talk with alternative survival pathways is not fully understood.

Epithelial-mesenchymal transition (EMT), an essential developmental process hijacked by cancer cells to enable their dedifferentiation and metastatic proliferation,[7] corresponds to poor prognosis in numerous malignancies, including prostate cancer. Several studies have indicated complex androgen signaling involvement in progression to EMT.[3,7] New avenues of investigation have focused on the potential impact of androgen blockade on drivers of EMT,[7] with speculation that low threshold levels of AR may promote metastasis.[3] Clinically, ADT has been associated with increased expression of EMT markers.[8,9] Progression to mCRPC has also been associated with activation of transforming growth factor-β (TGF-β) signaling,[10] a major pathway of EMT.[7] A novel finding recently published in *Science Signaling* by Chen et al. provides a promising mechanistic explanation for disease recurrence that links inactivated AR signaling by ADT to a TGF-β signaling associated pathway.[1] With the identification of SPDEF as an AR-regulated transcriptional repressor of TGFβ-induced protein (TGFBI), they suggest that castration resistance may be an unforeseen consequence of ADT resulting from collateral induction of EMT.

In their study, overexpression and knockdown of TGFBI in cultured prostate tumor cell lines and mouse xenograft models revealed a significant association between TGFBI and expression of EMT markers, with corresponding effects on cell proliferation, tumor growth, and metastatic lesion formation. The authors observed significantly more potent effects of TGFBI in AR-negative cells than AR-positive cells, indicating the possibility of TGFBI repression by AR signaling. They subsequently showed that siRNA knockdown of AR increased TGFBI transcription in AR-positive cells, while exogenous AR decreased TGFBI transcription in AR-negative cells. These effects were not diminished by TGF-β signaling modulation, suggesting an overriding mechanism of TGFBI repression by AR independent of traditional TGF-β signaling pathways. Treatment with AR agonist (DHT) or antagonist (enzalutamide) additionally confirmed AR-dependent repression of TGFBI.

The authors then sought to characterize potential upstream factors regulating the inhibition between AR and TGFBI. Gene set enrichment analysis identified SPDEF as a mediator of this interaction, in line with emerging evidence of its function as a tumor metastasis suppressor *in vivo*.[11] Analysis of clinical data sets also revealed TGFBI and SPDEF expression to be differentially enriched in AR-negative and AR-positive cells, respectively, while treatment with DHT or enzalutamide demonstrated activation of SPDEF in response to AR signaling. Importantly, TGFBI expression increased in response to SPDEF knockdown regardless of DHT treatment, placing SPDEF downstream of AR signaling. ChIP-seq analysis confirmed AR-dependent and site-specific binding of SPDEF in the TGFBI promoter. The authors further hypothesized a negative feedback loop of TGFBI itself on SPDEF, as exogenous TGFBI was sufficient to overcome the inhibitory effects of

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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.[8] 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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