The AR-DNA repair axis: insights into prostate cancer aggressiveness

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Despite significant advances in understanding the biology of advanced prostate cancer and approval of novel therapeutic agents, there is no durable cure for metastatic disease. Recent findings unmasked the importance of androgen receptor (AR) signaling in regulation of DNA repair, and alterations of the AR-DNA repair factor axis were shown to promote aggressive phenotypes including metastasis. These and related findings underscore the importance of determining impact AR-DNA repair factor alterations on prostate cancer progression.

Key Words: CRPC, androgen, DNA repair, DNA-PK, prostate cancer

Introduction

Prostate cancer remains the 2nd leading cause of cancer death in US men. Local prostatic adenocarcinoma can be effectively treated through radical prostatectomy or radiation therapy; however, non-organ-confined prostate cancer represents a major clinical challenge. First line treatment for non-organ confined disease consists of androgen deprivation therapy (ADT), as prostate cancer cells are exquisitely dependent on androgen receptor (AR) signaling for growth, survival, and as was recently shown, effective DNA repair. Notably, AR is a ligand-dependent transcription factor whose activity can be suppressed through pharmacological manipulation. ADT is elicited via GnRH agonists that suppress testicular androgen synthesis, (thus depleting AR of ligand), often complemented by use of direct AR antagonists. ADT is initially effective in the majority of patients, and successful suppression of AR activity is validated by loss of detectable prostate-specific antigen (PSA) in patient sera; PSA is encoded by a well-defined AR target gene, and serves as a biochemical readout of prostate-specific AR function. ADT results in a mixed population of tumor cell quiescence and cell death, resulting in remission. Unfortunately, this is transient (~2-3 years), and recurrent, "castrate-resistant" prostate cancer (CRPC) emerges for which there is no durable cure. This transition is driven by inappropriate AR reactivation in the majority of CRPC despite the continuation of ADT, leading to patient morbidity. Thus, it is critical to identify mechanisms beyond AR targeting, acting in concert with standard of care to either prevent or effectively manage CRPC.

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DNA repair alterations are frequent in advanced disease

Emerging data from multiple studies recently demonstrated that alterations in DNA damage repair (DDR) pathways are more common than previously thought in sporadic prostate cancer, and that DDR alterations likely afford new, more effective means of therapeutic intervention in a subset of advanced disease.[1-3] In an initial study which characterized the genomic landscape of metastatic CRPC (mCRPC), alterations of DDR genes were identified alterations in ~23% of cases, suggesting that dysregulation in DDR genes represents a significant driver of prostate cancer

progression.[4] While suggestive that these alterations may be pathogenic drivers of disease progression or aggressive features, this concept has not been formally assessed, which limits the understanding of the biological consequence of prevalent DNA repair alterations. The need to experimentally assess putative DNA repair driver alterations and generate models to discern tumor relevance is underscored by prediction analyses of reported DNA repair alterations in both primary prostatic adenocarcinoma and in mCRPC.

AR is a critical regulator of DNA repair in prostate cancer and CRPC

The importance of DNA repair regulation (and alterations thereof) was further heightened by discoveries which revealed the critical role of androgen/AR signaling in regulating DNA repair competency. Initial findings identified the androgen receptor (AR) as a requisite effector of double-strand DNA repair that alters the response to genotoxic insult in advanced prostate cancer.[5,6] This AR function proved dependent on the ability of AR to regulate expression and activity of DNAPK, an enzyme that is key for the process of repairing double-strand DNA breaks through non-homologous end joining, and has a parallel role as a transcriptional modulator.[5] The impact of AR in regulating DNA repair is dependent on AR-induced DNAPK expression and activity.[5] Further investigation demonstrated that AR-induced DNAPK activation promotes transcriptional networks that promote cell migration and metastasis, thus linking the AR-DNA repair axis to tumor progression and acquisition of aggressive tumor phenotypes.[3] Strikingly, DNAPK is the most deregulated kinase in metastatic CRPC, and is independently predictive of metastasis and overall survival in patients with high risk disease.[5] These findings not only nominate DNAPK as a biomarker to predict which tumors will go on to develop metastases, but identify DNAPK as a therapeutic target to treat or prevent advanced disease. Based on these studies, a clinical trial study is ongoing which will assess the impact of a DNAPK inhibitor (CC-115) in combination with Enzalutamide. Preclinical investigation showed that targeting DNAPK enhances response to AR-directed therapies, using both in vivo xenografts and ex vivo culture of primary human tumors.[7] Combined, these studies strongly suggest that leveraging the dual functions of DNAPK in promoting DNA repair and metastatic progression will improve outcomes for advanced disease. Additional AR-dependent DDR factors (e.g. Ku70) have also been identified, which likely contribute to the impact of androgens/AR in promoting DNA break repair.[8] Given these substantial functions and the association of AR-DDR axis perturbations with aggressive disease, determining the impact DDR alterations (both somatic and germline) on AR-mediated DNA repair will be critical for assessing the contribution of these genetic alterations to prostate cancer development and progression.

Disclosures

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