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Uncovering the genetic landscape driving castration-resistant prostate cancer

Timothy J. Martin, Cody J. Peer and William D. Figg*

Clinical Pharmacology Program; Medical Oncology Branch; Office of the Clinical Director; National Cancer Institute; Bethesda, MD USA

Identification of the mechanisms that drive progression of metastatic castration-resistant prostate cancer (CRPC) has fostered interest since early androgen studies in the 1940s. Little knowledge has surfaced about the role mutations play in prostate cancer development. A group at the Michigan Center for Translation Pathology studied exomes of lethal, metastatic CRPC and documented the overall mutation rates. In classifying these mutations, the monoclonal cause of CRPC was recognized. Nine identified genes showed significant mutations. Six of these genes had previously been reported as mutated in prostate cancer. The analysis also found significantly mutated androgen receptor (AR) cofactors and linked proteins, including FOXA1 and MLL2. Another finding concerned an aberration in CHD1. Prostate cancers with deletions or mutations in CHD1 showed a strong correlation with ETS gene family fusion negative prostate cancers (96%). In profiling these exomes, this group provides an original method to identify deletions and mutations that drive CRPC progression.

Keywords: castration-resistant prostate cancer, mutations, genetics

Abbreviations: CRPC, castration-resistant prostate cancer; AR, androgen receptor; FOXA1, fork-head box protein A1; MLL2, mixed-lineage leukemia protein 2; CHD1, chromodomain helicase DNA binding protein 1; ETS, E-twenty-six; PTEN, phosphatase and tensin homolog

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*Correspondence to: William D. Figg;
Email: wdfigg@helix.nih.gov:

Treatment of metastatic prostate cancer via androgen-deprivation yields optimistic results, yet almost every case devolves to a state of castration-resistant prostate cancer (CRPC).[1] Numerous mechanisms, including gene fusions and chromosomal rearrangements, have previously demonstrated the eventual progression of these metastatic cancers to achieve castration-resistant states.[2] Among these mechanisms are ETS fusions, PTEN loss and amplification of the androgen receptor the (AR).[3] Recent studies have recognized a wider variety of recurrent mutations in proteins that interact with the androgen receptor.[3] Due to the limited amount of knowledge surrounding the mutational spectrum of prostate cancer, there is a need to further understand the roles that these recurring mutations play in CRPC progression.

Grasso et al.,[3] published in *Nature*, sequenced exomes of 50 cases of patients with CRPC. Nine genes were significantly mutated. Of those nine, six have previously been known as mutated in prostate cancer: TP53, AR, ZFHX3, RB1, PTEN and APC.[3] Three other genes, OR5L1, CDK12 and MLL2, previously thought to have no connection to prostate cancer, showed significant mutations as well. OR5L1, an olfactory gene, has a high mutation rate due to its late replication, but shows no role in cancer.[3] CDK12, significantly mutated in ovarian serous carcinoma, can cause resistance to tamoxifen and estrogen deprivation when silenced. MLL2, a coactivator of the estrogen receptor, encodes H3K4, a histone methyltransferase frequently mutated in lymphomas and carcinomas.[4] While DNA methylation leads to gene silencing, histone methylation can trigger gene activation or inactivation. Mutations in histone genes are not frequent in prostate cancers, but the aberrant chromatin or histone may interact and interfere with AR signaling.[5]

New evidence links the ETS family of transcription factors to carcinogenesis regulation as well as AR transcriptional activity.[6] This association explains the link to prostate cancer development. A rise in

ETS1 activity marks poor prognosis and conveys abnormal regulation of many cancer-linked genes. This poor transcriptional regulation results in enhanced cell survival, cell growth, angiogenesis, migration and invasion.[6] The authors recognized CHD1 deletions or mutations in 10 of 119 (8.4%) of the analyzed exomes. These mutations and deletions are significantly linked to ETS deleted status. Fifty of the 954 (5.2%) prostate cancer cases were CHD1 deleted. Forty-eight of those 50 (96%) CDH1 deleted cases also had ETS deletions providing evidence that CHD1 deletion and mutation are defining factors in ETS deleted prostate cancer.[3] Deletion and mutation of ETS2 are characteristic of prostate cancer progression as well. Mutated ETS2 significantly increased cell proliferation, migration and invasion relative to wild-type ETS2.[3] This tumor suppressor gene is deleted in roughly one-third of all CRPCs.[7] Gene deregulations sometimes occur via mutation, however in the case of ETS2, the TMPRSS2: ERG fusion is the cause of this gene deletion.[3,8]

Another significantly mutated pathway was observed in the PTEN network. Loss of PTEN reduces androgen-sensitive gene expressions through the regulation of AR transcription.[3] Thus, prostate cancers initiated by PTEN loss result in suppression of AR transcription output and can progress to CRPC independent of epithelial AR. Upwards of 70% of late stage prostate cancer exhibit the loss of PTEN.[9]

The authors took a closer look at a documented 2 bp insert in FOXA1. FOXA1, from the forkhead box transcription factor family, acts as a cofactor for steroid receptor binding.[10] FOXA1 controls AR and estrogen receptor (ER) regulated hormones in prostate cancer cells and breast cancer cells, respectively.[10] Although only 5 of 147 (3.4%) screened prostate cancer lines showed FOXA1 mutation, these mutations in an AR cofactor are important due to the crucial role of AR in CRPC signaling.[3] Further, the authors showed siRNA knockdown of FOXA1 yields decreased growth in LNCaP cells.[3,10]

While we have made significant strides in understanding the biology of prostate cancer over the past 25 years, much knowledge of the spectrum of prostate cancer genetics remains unidentified. Future studies are indeed necessary to help shape this mutational background of prostate cancer progression. This study demonstrated that involving genetic sequencing could offer a new and unique insight for potentially classifying new therapies in late stage cancers and discovered known and novel gene mutations that may be at the root of the various mechanisms driving lethal prostate cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Note

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