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RESEARCH HIGHLIGHT

Mapping mutations in prostate cancer exomes

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Comprehensive identification of driver mutations in prostate cancer can serve to enhance our understanding of the disease and expand the use of available treatment options. Two recent and complementary studies from Barbieri *et al.*[1] and Grasso *et al.*[2] have reported the results of exome sequencing analysis in large cohorts of primary, treatment-naïve and lethal castration-resistant prostate cancer (CRPC) cases, respectively. Together, these analyses revealed a number of novel genetic mutations representing uncharacterized drivers as well as combinations of mutations that may define important prostate cancer subtypes.[1,2]

The heterogeneity of genomic instability in human cancers confers upon these lesions a broad range of advantageous growth and invasive qualities. Several common genetic abnormalities with clear roles in facilitating prostate cancer development and progression have been described previously. Copy number losses in the *PTEN* tumor suppressor are common across prostate cancers of broad-ranging severity,[3] while copy number gains in the androgen receptor (AR) are frequently observed and underscore the importance of the androgen signaling axis in both primary prostate cancer and CRPC.[3] As many as 75% of prostate cancers harbor a rearrangement involving the upstream regulatory elements of *TMPRSS2* (an AR regulatory target) and the coding region of an *ETS* family transcription factor (e.g., *TMPRSS2-ERG* fusion gene), further demonstrating the essential nature of AR signaling in the expression of oncogenic gene targets driving prostate tumorigenesis.[3,4] While these prototypical genetic aberrations including copy number changes and gene fusions reveal the mechanism of several growth and invasive strategies acquired by prostate cancers, less is known about the role of gene mutations in prostate tumorigenesis. The current investigations provide several candidates genes whose mutation may drive specific prostate cancer cases and which may identify aberrant pathways with therapeutic value.

Copy number loss and mutations of *CHD1*, encoding a chromatin-remodeling enzyme, were observed in each study.[1,2] *CHD1* was previously characterized by deregulation in prostate cancers,[5] representing a pathway for dedifferentiation of tumor cells. Importantly, both studies independently correlate the loss or mutation of *CHD1* (*CHD1*$^-$) with a *TMPRSS2–ETS* fusion-negative state. Barbieri *et al.* further correlated the *CHD1*$^-$/fusion-negative genotype with mutations in *SPOP*, a gene encoding an E3 ubiquitin ligase subunit. *SPOP* mutations have been previously reported by the Garraway group in a small cohort of primary prostate cancer samples[5] and may represent a prostate cancer-specific mutation as observed by Kan *et al.*[6] in their study of candidate gene mutations across 441 diverse cancers. In CRPC cell line models, mutant-*SPOP* or *SPOP* small interfering RNA transfection leads to enhanced cell invasion without affecting cell proliferation.[1] In much the same way that *TMPRSS2–ERG* collaborates with *PTEN* loss or chromosome 3p14 deletion to drive prostate cancer development,[4] *CHD1*$^-$ may cooperate with *SPOP* mutations to initiate *TMPRSS2–ETS* fusion-negative prostate tumorigenesis.

The role of FOXA1 as a pioneering factor for AR-mediated transcriptional regulation and in an AR-independent transcriptional network in prostate cancer is currently understood.[7] However, the nature and prevalence of *FOXA1* mutations in prostate cancer has not been comprehensively studied. The present analyses have revealed that *FOXA1* mutation occurs at a rate of 3%–4% among primary prostate cancer and CRPC cases. Interestingly, mutations clustered either to the C-terminal domain, responsible for histone interactions that result in chromatin relaxation, or to the DNA-binding domain.[1,2] Thus, inactivating mutations in *FOXA1* may affect FOXA1 chromatin binding and the expression of FOXA1 target genes involved in important biological processes. Indeed, Grasso *et al.*[2] demonstrated that specific *FOXA1* mutations uniquely modulate AR transcriptional programs and prostate cancer cell proliferation, as mutant-*FOXA1* transfection in LNCaP cells either enhances or inhibits proliferation depending on the identity of the mutation. This leads to the possible utility of *FOXA1* mutation status as a prognostic marker capable of identifying cancers with aggressive growth characteristics. Differentiation between the gene targets of mutant and wild-type FOXA1 may reveal important signaling pathways unique to prostate cancer subtypes, informing the application of targeted therapies against mutation status-specific FOXA1-regulated genes. One such target gene, *CDKN1B*, was also found to exhibit somatic mutations in primary tumor samples. While previous germline mutations have been reported,[8] Barbieri *et al.*[1] reported that this cyclin-dependent kinase inhibitor was deleted in 16 and mutated in 3 tumor samples of the 111 tumors examined. Together, *FOXA1* mutations and/or *CDKN1B* mutations provide a mechanism for growth deregulation in these prostate cancer subtypes.

An additional class of mutations with the potential to affect transcription mediated by FOXA1 was observed by Grasso *et al.*[2] The MLL complex exhibits methyltransferase activity and has a demonstrated role in establishing histone H3 lysine 4 methylation patterns.[9] Histone H3 lysine 4 methylation is known to act upstream of FOXA1, directing this pioneer factor to specific binding sites

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where it regulates expression of target genes including $G_{1/S}$ and $G_{2/M}$ cell cycle genes.[10,11] Therefore, mutations of MLL complex subunits may deregulate FOXA1 transcriptional networks.

Finally, Barbieri *et al.* identified *MED12* mutations in a small subset of primary prostate cancers. MED12 is a subunit of the kinase module of the Mediator coregulatory complex that interacts with multiple transcription factors involved in a wide range of signaling pathways.[12] The Mediator complex has been shown to play an essential role in a large proportion of eukaryotic transcriptional events including chromatin looping.[4,13] In fact, the indispensable role of MED1 in chromatin-loop formation at the *UBE2C* locus is known to deregulate the metaphase-anaphase transition in CRPC.[14] Since MED12 has been found to mediate enhancer-promoter looping in other systems,[13] *MED12* mutations may affect the formation of chromatin loops and subsequent target gene expression in prostate cancer. In a previous study identifying a number of frequent *MED12* mutations in uterine leiomyomas, pathway analysis of genes differentially expressed in *MED12*-mutant cases revealed alterations in focal adhesion, extra cellular matrix interaction and Wnt signaling pathways.[15]

The mutations identified in these studies may inform the development of new strategies in prostate cancer treatment or the novel application of existing therapeutics. *FOXA1* mutations result in an altered target gene expression profile,[2] possibly promoting cancer cell proliferation *via* deregulation of oncogenic transcriptional targets or repression of cell cycle regulatory targets. *SPOP* mutations may influence substrate specificity, resulting in differential degradation of proteins with potential carcinogenic or tumor suppressive roles.[1] While targeting transcription factors has proven difficult[16] and targeting chromatin remodelers, histone methyltransferases and ubiquitin ligases may result in undesirable off-target effects, the clinical application of these findings will likely require identification of the pathways altered in the presence of these mutations. This approach is exemplified in a recent study of non-small cell lung cancer in which targeted therapies were implemented against GATA2 downstream activities including the proteasome and Rho signaling, resulting in substantial tumor regression in mice.[17] Finally, the identification of prostate cancer subtypes (e.g., *CHD1*$^{-}$/*SPOP* mutations/*TMPRSS2* fusion-negative) may prove valuable in differentiating patient populations based on mutation and gene fusion status. Future work on stratifying disease categories along these lines could define distinct subtypes with different prognoses, provide opportunities for development of novel therapeutic agents and enhance the precision of our treatment strategies.

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