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RESEARCH HIGHLIGHT

A picture with more details is painted for prostate cancer

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By comparing all gene-coding sequences in the genome between tumors and matched normal samples from clinically localized and castration-resistant (CR) prostate cancer patients, two groups of scientists have recently identified more than 5000 somatic mutations.[1,2] These findings are important because they add another dimension of somatic DNA alterations in the genome of prostate tumors. Together with other known acquired DNA alterations in prostate tumors such as deletions, amplifications and fusions,[3–6] they provide insights into the mechanisms of tumorigenesis and cancer progression of this heterogeneous disease. Some of the important findings are highlighted below.

SOMATIC MUTATION RATE IN PROSTATE TUMORS IS HIGHER THAN PREVIOUSLY ESTIMATED

It is commonly believed that point mutation is less prevalent in prostate tumors and was estimated at 0.33 Mb^{-1}.[7] In these two studies, the average mutation rate was estimated at 1.4 Mb^{-1} in 112 untreated localized prostate tumors[1] and 2.0 Mb^{-1} in 50 heavily treated castration-resistant (CR) tumors.[2] The higher mutation rate than previously estimated may reflect, at least in part, increased sequence coverage in these two studies. However, compared with other major human cancers, somatic mutation rate in prostate tumors remains generally low.[7]

COMMONLY AND SIGNIFICANTLY MUTATED GENES IN PROSTATE TUMORS

Although genes with recurrent mutations in prostate tumors have been documented (http://www.sanger.ac.uk/genetics/CGP/cosmic), they were based on candidate genes thought important in cancer development. Results from these two new reports, for the first time, present a comprehensive and objective list of the most commonly mutated genes in the genome of prostate tumors. Furthermore, each of these genes reached statistical significance, i.e., observed number of mutation is significantly higher than expected by chance given gene size, sequence context and frequency of mutations in each tumor. For localized prostate tumors, the 12 most significantly mutated genes are *SPOP*, *FOXA1*, *TP53*, *PTEN*, *CDKN1B*, *MED12*, *THSD7B*, *SCN11A*, *NIPA2*, *PIK3CA*, ZNF595 and *C14orf49*.[1] *SPOP* was the most commonly mutated gene in these tumors, with a frequency of 13%. For CR tumors, the nine most significantly mutated genes include *TP53*, *ZFHX3*, *RB1*, *PTEN*, *APC*, *AR*, *MLL2*, *OR5L1* and *CDK12*.[2] *TP53* was at the top in this group, with a frequency of 40%.

COMMONALITY AND UNIQUENESS OF MUTATED GENES IN THESE TWO TYPES OF TUMORS

PTEN and *TP53* were the only genes significantly mutated in both localized and CR tumors in these two studies, emphasizing their broad roles in cancer initiation, progression and treatment resistance. For majority of the remaining genes, recurrent mutations were also found in both types of tumors, although statistical significance was reached in only one type of these tumors. There are, however, several exceptions. *PIK3CA*, *ZNF595* and *C14orf49* were significantly mutated in localized prostate tumors but no mutation in these genes was observed in CR cancer, suggesting that mutations of these genes unlikely play an important role in the development of lethal CR prostate cancer. On the other hand, of the nine significantly mutated genes in CR tumors, mutation in three genes (*AR*, *RB1* and *CDK12*) was not found in localized prostate tumors. Mutations of these genes in CR tumors may be triggered in response to hormone therapy, or reflect selection advantage for lethal CR prostate cancer.

TWO TYPES OF MUTUALLY EXCLUSIVE PROSTATE TUMORS

By examining tumors with *SPOP* mutations, Barbieri *et al.*[1] found that none of these tumors carried ETS family gene rearrangement. Furthermore, they found that tumors with SPOP mutations were positively associated with deletion of *CHD1* at 5q21.1 and deletions of *FOXO3* and *PRDM1* at 6q21. Based on these observations, Barbieri *et al.*[1] proposed that *SPOP* mutations may define a new molecular subtype of prostate cancer. Similarly, using an integrated analysis of exome sequencing, copy number and expression, Grasso *et al.*[2] found an inverse association between ETS family gene rearrangement and focal deletion or mutation of *CHD1*. Therefore, both studies suggest two distinct and mutually exclusive prostate cancers: (i) tumors with ETS family gene rearrangement, and (ii) tumors with deletions or mutations at *CHD1*/*SPOP*. It is, however, unclear whether *CHD1* or *SPOP* defines the second subtype of prostate cancer. It is noted that deletion of *CHD1* was previously reported to be inversely associated with the genomic deletion that resulted in *TMPRESS–ERG* in localized prostate tumors.[8]

FOXA1 AND CHROMATIN/HISTONE-MODIFYING GENES PHYSICALLY INTERACT WITH AND FUNCTIONALLY REGULATE AR

In the mutational landscape of CR prostate cancer identified by Grasso *et al.*, it is noteworthy that multiple recurrently mutated

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genes are commonly involved in the modulation of androgen–AR signaling.[2] Besides alterations that are directly associated with deregulated androgen synthesis (e.g. *CYP11B1* amplification) and signaling (e.g. *AR* amplification/mutation, point mutations of *NKX3-1*), recurrent copy number and mutational alterations were also identified in genes whose protein products have been demonstrated to physically interact with and functionally regulate AR. Among these genes include the AR collaborating factor *FOXA1*, whose mutations were found in 3.4% of prostate cancer patients and whose mutant forms were shown to repress androgen signaling and increase tumor growth. In addition, recurrent mutations were notably found in multiple chromatin/histone-modifying genes, including *MLL2* (mutated in 8.6% of prostate cancer), *ASXL1* and *UTX*, which also interact with and regulate AR signaling. These findings together suggest that the aberrant androgen–AR signaling caused by alterations of these recurrently mutated genes may serve as at least one common mechanism underlying the castration resistance phenotype exhibited by almost all prostate cancer patients undergoing hormonal therapy.

ETS2 IS A CANDIDATE TUMOR-SUPPRESSOR GENE

An important finding in the study of Grasso *et al.* is somatic alterations at *ETS2* and their role in prostate cancer development and invasion. *ETS2*, located between *TMPRESS2* and *ERG*, is deleted in one-third of prostate cancers and mutated in a CR tumor. Its tumor-suppressor role was also suggested from the observation that tumors with *TMPRESS–ERG* fusions through deletion were more aggressive than those through translocation. More importantly, the tumor-suppressing function of *ETS2* was suggested by the demonstration that overexpression of wild-type *ETS2* led to decreased cell proliferation, migration and invasion, and that mutant *ETS2* had opposite effects.

Future studies should be extended to intergenic/noncoding regions in the genome to better define chromosomal rearrangements, including types, boundary, and frequency of deletions, gains and fusions. These types of alterations are important in prostate tumors but were only examined using low-resolution methods such as array-comparative genomic hybridization and genome-wide single-nucleotide polymorphism arrays or in a few samples using whole-genome analysis.[3] In addition, greater efforts should be devoted to assessing correlation of somatic alterations with clinical presentations.

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