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Review article

# High-risk prostate cancer: A disease of genomic instability

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**Abstract**

**Objectives:** In this review, we will discuss the latest advances in our understanding of the relationship between the cellular DNA damage response and genomic instability in prostate cancer and the emerging possibilities to exploit these aberrations as prognostic biomarkers and guides for personalized patient management.

**Methods:** Important findings related to genomic instability in prostate cancer were retrieved from the literature and combined with our own results and a translational perspective.

**Results:** Prostate cancer is characterized by a highly altered genomic landscape with a wide spectrum of genomic alterations, including somatic mutations, copy number alterations (CNAs), gene fusions, complex chromosomal rearrangements, and aneuploidy. In addition, massive DNA damaging events, including chromothripsis and chromoplexy, which can lead to extensive genomic insults in a single step, have been identified. A number of these genomic aberrations have been found to provide prognostic information and can therefore help to identify high-risk patients. In addition, defects in the DNA damage checkpoint and repair machinery can potentially be harnessed for therapeutic purposes.

**Conclusions:** Genomic instability plays a crucial role in the malignant progression of prostate cancer and can be exploited for the development of novel prognostic biomarkers and innovative therapies. 

*Keywords:* Prostate cancer; Genomic instability; Somatic mutations; DNA damage; Translational therapeutics; Biomarkers

## 1. Introduction

Prostate cancer is a heterogenous disease. Although most prostate cancers are treatable and have a low risk for disease recurrence, some tumors show aggressive growth and an unfavorable clinical outcome. During the past several years, a number of studies have lent vital support to the notion that the biological differences between indolent and aggressive prostate cancers involve genomic instability [1].

Genomic instability is both a state and a process and comprises various genetic alterations of cancer genomes that can develop with different dynamics. In prostate cancer, these genetic changes include the entire spectrum of known alterations such as somatic mutations, small inversions or deletions, copy number alterations (CNAs), gene fusions, interchromosomal and intrachromosomal rearrangements, as well as extensive genome-damaging events such as chromothripsis or chromoplexy, and finally, whole chromosome CNAs (aneuploidy) [1–3]. Genomic instability is a critical factor for the creation of variants within a tumor cell population. It therefore drives clonal evolution, intratumoral and intertumoral heterogeneity, malignant progression, and ultimately therapy resistance [4]. The rate at which these alterations develop is also an important aspect as it is now known that single catastrophic events that affect multiple genes can occur in prostate cancer and may hence superimpose the gradual acquisition of genetic abnormalities [2,5].

There are, nevertheless, some caveats to the general notion that an unstable tumor cell genome per se drives malignant progression. There are a number of examples in

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which deficiency in certain genes that promote genomic instability can also lead to overwhelming genomic damage and are therefore not compatible with cell viability but instead lead to cellular senescence or cell death [4]. It has furthermore been shown that growth factors and other factors produced by the tumor microenvironment can potentially shape prostate cancer genomes [6,7]. Hence, genomic instability is not only a cancer cell–intrinsic process but is subject to modulation by external factors.

The interplay between genomic plasticity and selection barriers ultimately results in an enormous collection of coexisting tumor cell subclones. This can either thwart therapeutic interventions because of pre-existing resistant variants as pointed out before or can potentially be harnessed for new therapeutic opportunities, for example, synthetic lethal approaches [8]. Therefore, genomic alterations in prostate cancer have important clinical implications as they can be used for patient stratification and for the identification of novel drug targets.

Here, we review the recent advances in the understanding of prostate cancer genome evolution and the translational implications of these findings. We also briefly describe possible underlying molecular mechanisms that can generate genomic instability, emphasizing the fact that our understanding of how these widespread genomic changes arise is still incomplete.

## 2. The mutational "landscape" of localized and advanced prostate cancer

A number of deep sequencing studies have collectively shown that the somatic mutation rate in prostate cancer is in the medium to lower range. The average frequency of gene mutations was 0.31 mutations/Mb in an exemplary study [1], which is significantly lower in comparison with other tumor entities such as lung squamous cell carcinoma (8.4 mutations/Mb) [9] or malignant melanoma (30 mutations/Mb) [10]. Even between localized and advanced prostate cancers, the increase of the somatic mutation frequency is relatively moderate [11]. In very rare cases, however, thousands of mutations per exome have been reported, which may reflect the acquisition of a mutator phenotype through mutations in DNA polymerases or DNA repair genes such as MSH6 [12,13].

The spectrum of genes recurrently altered by somatic mutations compromises several important tumor suppressor genes and oncogenes such as *TP53*, *RB1*, *PTEN*, *MYC*, *PIK3CA*, and *SPOP*; various histone-modifying genes; genes involved in transcriptional control; and, as a unique feature of prostate cancer, the androgen receptor (*AR*) gene (see Table for the most common somatic mutations in prostate cancer) [11,13–15]. Remarkably, somatic driver mutations in genes that are potentially targetable with currently available small molecule inhibitors, such as receptor tyrosine kinase inhibitors, are comparatively rare, but, for example, *BRAF* mutations have been reported in a small number of tumors [1].

Variations in *AR* gene expression, including both gene mutations and amplifications, are among the most frequently reported genomic alterations in prostate cancer and contribute importantly to the development of castration-resistant prostate cancer (CRPC) [1]. Mutations in AR cofactors such as *FOXA1*, a known AR-interacting protein, have also been discovered [11]. Together, these findings further underscore the key role of AR signaling in prostate cancer progression on a genetic level. Interestingly, deregulation of AR signaling has also been implicated as a driver of genomic instability [16]. Tumor genomes from patients with early-onset prostate cancer who were 50 years or younger were found to have significantly more structural gene rearrangements that affected androgen-regulated genes together with significantly increased AR expression levels. These results underscore the role of androgen signaling as a driver of genomic aberrations, particularly in younger patients [16,17]. Furthermore, a direct role of AR signaling in the regulation of DNA repair has recently been suggested [18,19]. AR signaling was found to stimulate the expression of a number of DNA repair genes, which can impair the effectiveness of radiation therapy. These findings explain the clinical benefit of adding androgen-deprivation therapy to radiotherapy to treat prostate cancer [18,19].

Efforts to harness somatic mutations and other genomic alterations for patient risk stratification are ongoing. A newly identified subset of prostate cancers has been reported to harbor mutations in the gene encoding *SPOP*, a substrate-recognition subunit of a class of cullin E3-ubiquitin ligases [13,14]. Remarkably, these tumors do not harbor a common chromosomal rearrangement involving the E26 transformation-specific (ETS) family of transcription factors. This subset of *SPOP*-mutated, ETS-related gene (ERG) rearrangement–negative prostate cancers was enriched for deletions of chromosomal regions harboring the *CHD1* (5q21) and *FOXO3* (6q21) genes and was found to typically lack alterations in *TP53*, *PTEN*, and *PIK3CA* [13]. Additional studies are needed to determine if this genomics-based patient stratification has prognostic relevance or predicts treatment responses.

Besides genes that can lead to a hypermutation phenotype, there are additional classes of genes that function as "caretakers" [4] of DNA integrity and can hence lead to detrimental consequences when genetically inactivated. For instance, mutations affecting the DNA damage response and repair genes *BRCA1/2* or *ATM* have been reported in prostate cancer [15]. The presence of germline *BRCA1* or *BRCA2* mutations has been shown to increase the prostate cancer risk by 3.5-fold and 8.6-fold, respectively [20,21]. In the case of *BRCA1*, both somatic and germline losses have been found to be associated with more aggressive tumor characteristics [22,23]. Other recurrently mutated genes with a role in the cellular DNA damage response include chromatin modifiers such as members of the MLL complex and CHD1 [11,14].