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Revisiting the Role of p53 in Prostate Cancer

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Abstract: Mutations in the tumor suppressor gene *TP53* are among the most common genetic aberrations in cancer. In prostate cancer, the role of mutant *TP53* remains incompletely understood. Initially, mutations in *TP53* were considered late events during malignant progression and associated with metastatic dissemination and castration resistance. However, recent studies report an inactivation of *TP53* at an unexpectedly high frequency in primary as well as metastatic castration-naïve prostate cancer. In this chapter, we discuss the biology of p53, the relevance of *TP53* mutations for prostate cancer progression and therapy

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resistance, and its potential role as a marker to identify patients who require more intensified treatment.

Keywords: castration-naïve prostate cancer; castration-resistant prostate cancer; p53, therapy resistance; *TP53*

INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer in men (1). Due to the introduction of broader screening and testing for prostate-specific antigen (PSA) blood levels, the majority of prostate cancers are now diagnosed at a localized state (2). Prostate cancer is a heterogeneous disease, and the clinical outcome of localized prostate cancer is highly variable. Approximately 30% of men suffer from relapse despite definitive local treatment by radical prostatectomy or percutaneous radiotherapy (3). Localized prostate carcinoma already shows a substantial molecular and genetic diversity (4). There is hence an urgent clinical need to identify molecular and genetic markers with predictive and prognostic relevance in addition to "classical" outcome parameters such as TNM stage, Gleason score and initial PSA level (5). A better characterization of genetic factors associated with more aggressive tumor growth kinetics could influence clinical decision-making with respect to more personalized neoadjuvant and/or adjuvant strategies (6).

The finding that a significant proportion of men with advanced prostate cancer harbor germline and/or somatic mutations in DNA damage repair genes has been a major advancement in the management of the disease (7). It has been known for a while that tumors with DNA damage repair gene defects are associated with earlier metastatic dissemination and poorer disease outcome (8–11). At the same time, mutations, in particular in *BRCA1* and *BRCA2,* create a therapeutic vulnerability that has been exploited by the use of PARP inhibitors in patients with metastatic, castration-resistant prostate cancer (mCRPC) (11, 12). Recent results from several phase II and III trials confirm a clinical advantage of PARP inhibition in terms of progression-free and overall survival (12–18). However, there is mounting evidence that not all patients who are broadly categorized as carrying DNA damage repair gene defects (in fact many of these genes play only indirect roles in DNA damage repair) benefit from PARP inhibition (19). Therefore, additional molecular markers are needed to characterize therapeutic vulnerabilities, treatment resistance and patient prognosis with an even higher resolution.

A gene that is typically not included in targeted next-generation sequencing (NGS) panels used in key phase II and III trials to identify patients for PARP inhibitor treatment is *TP53*, one of the most frequently altered tumor suppressor genes in human cancer.

THE EVOLUTION AND FUNCTION OF p53

p53 was first discovered in 1979 and initially thought to be an oncogene (20–24). Subsequent work demonstrated that the transcription factor p53, together with

its E3 ubiquitin ligase MDM2, is at the center of a signaling node that plays a crucial role in stress response and tissue homeostasis (25). Over hundreds of millions of years, the p53 family has evolved from protecting the germline of invertebrates from mutations to a more general signaling hub that preserves the tissue integrity of vertebrates (25). p53 responds to a diverse array of cellular stresses by activating the transcription of genes that either lead to a reconstitution of the damaged cell or its elimination by apoptosis or cellular senescence (26). p53-dependent transcription hence promotes cell cycle arrest, DNA repair, metabolic adaptation, or the upregulation of pro-apoptotic genes such as *BAX* or *PUMA* or pro-senescence genes such as *PML* or *CDKN1A*. These properties as key regulator of cell fate decision make p53 the single most critical human tumor suppressor and contribute to the fact that *TP53* is the most commonly altered gene in human cancer (27, 28).

Physiologically, p53 is expressed at a low level in most normal cells, which involves a number of cellular antagonists, most importantly its E3 ubiquitin ligase MDM2 and its heterodimerization partner, MDM4 (29). By ubiquitinating p53, MDM2 drives the proteasomal degradation of p53 (30). MDM2 itself is positively regulated by p53 thus creating a feedback loop to ensure low p53 protein levels in the absence of cellular stress. Over a dozen of extrinsic and intrinsic stress signals have been reported to feed into the MDM2-p53 signaling node to cause activation of p53-dependent gene transcription (25). The p53 response is activated by decreased degradation upon disruption of the p53/MDM2/MDM4 complex leading to p53 stabilization. The disruption of these interactions is regulated by posttranslational modifications of MDM2 and/or p53 such as phosphorylation by protein kinases activated by stress such as ATR, ATM, CHK1, CHK2 or DNA-PK, among others (25, 31). Additional mechanisms of p53 activation exist such as the nucleolar sequestration of MDM2 by ARF in response to oncogene stress (32). Another mechanism of activation of the MDM2-p53 node involves the deubiquitinating enzyme HAUSP (33). Obviously, different sources of cellular stress can trigger distinct modes of p53 activation depending on the responding protein kinases.

Upon its activation, p53 binds to the promoter of p53-responsive target genes to activate gene transcription. MDM2 and MDM4 are co-recruited to these promoters where they form a complex with p53 to modulate target gene activation (34).

STRUCTURE OF p53

The tumor suppressor gene *TP53* encodes a protein with 393 amino acids and is located on chromosome 17p13.1 (35). The p53 protein comprises an N-terminal transactivation domain, a proline-rich domain, a central DNA-binding domain, followed by a tetramerization domain and an intrinsically disordered C-terminal regulatory domain (36). Inactivating mutations in *TP53* occur in approximately 50% of human cancers, and mutation rates range between more than 90% and below 5% depending on the tumor type (37). Most mutations are detected in the central DNA-binding domain, thereby incapacitating the function of p53 as a transcription factor. Missense mutations, frameshift deletions and frameshift

insertions account for approximately 70% of pathogenic mutations (37). Inactivation of both *TP53* alleles is found in over 90% of cancers with *TP53* mutations, most commonly through a single missense mutation and loss of the second allele through a deletion of chromosome 17p (37). Missense mutations frequently lead to an impaired degradation by MDM2 thus stabilizing the protein and rendering it easily detectable as overexpressed by immunohistochemistry (38). Remarkably, the top hotspot missense mutations occur at methylated CpG sites, which encode evolutionary conserved arginine residues. The most common mutation is R175H, followed by R248Q, R273H, R248W, R273C, and R282W, which account for approximately a quarter of all *TP53* missense mutations (39). As a functional consequence of these mutations, the transcriptional activation of p53-specific target genes is disrupted (40, 41) although gain-of-function mutations have also been described (42).

In addition to acquired mutations, germline mutations of *TP53* have been identified in patients with Li-Fraumeni syndrome. The Li-Fraumeni syndrome is characterized by sarcomas, breast and adrenal cortex carcinomas, cerebral tumors, and acute leukemias at a young age (43, 44). Germline mutations in *TP53* are highly penetrant with an up to 100% cumulative lifetime risk to develop cancer (45).

TP53 MUTATIONS IN PROSTATE CANCER

Initially, inactivation of *TP53* has been suggested to be a late event during prostate cancer progression (46–49). While it is now firmly established that mCRPC has the highest *TP53* mutations rates (see below), there is emerging evidence that *TP53* mutations can also be found at a relatively high frequency in primary, and, especially, in castration-naïve metastatic prostate cancer (50–56).

In the TCGA cohort, whole genome sequencing of 333 samples from men with localized prostate cancer was performed and a mutation rate in *TP53* of 8% was detected (51). In a different study, sequencing of 111 cases of primary prostate cancer revealed a *TP53* mutation rate of 6% (57).

Remarkably, the rate of *TP53* mutations in castration-naïve metastatic prostate cancer was between 28% and 36% and hence significantly higher than in primary prostate cancer (50, 52, 58) and only exceeded by mutation rates found in mCRPC. Analysis of 150 mCRPC samples showed a *TP53* mutation rate of 53% (59). In additional studies, the *TP53* mutation rate was between 31% and 73% (53, 60–63). Whole-exome sequencing data from 410 mCRPCs identified 33% of tumors with a biallelic loss of *TP53* and 32% with single-copy loss or a pathogenic mutation (62). These findings confirm the marked differences in the *TP53* mutation rate in primary, metastatic castration-naïve and castration-resistant prostate cancer.

Important insights into the role of *TP53* deficiency in disease progression stem from studies that incorporate patient outcome measurements and longitudinal studies. Hamid and colleagues showed that *TP53* alterations increase from localized castration-naïve prostate cancer (20%) to metastatic castration-naïve prostate cancer (37%) and mCRPC (73%) and are associated with an approximately 2-fold risk for disease recurrence in patients with primary prostate cancer (53). In a recent

study by Mateo and colleagues, primary prostate cancer specimens from 175 patients who later developed mCRPC were analyzed. Mutations and homozygous loss of *TP53* were the most frequently detected aberrations and found in 25% of the primary tumors (52). In addition, there appears to be an increase of *TP53* alterations, besides alterations of the androgen receptor (AR) pathway, when same-patient specimens obtained from the untreated primary tumor and mCRPC were compared (52).

In conclusion, there is emerging evidence for a high rate of *TP53* mutations in primary prostate cancer predisposed to a lethal disease outcome as well as prostate cancer with metastatic dissemination at the time of diagnosis.

p53 AND RESISTANCE OF PROSTATE CANCER TO SYSTEMIC THERAPY

Prostate cancer growth and progression exquisitely depends on androgens, and androgen deprivation still remains the most important treatment modality for patients with recurrent or metastatic disease (64). However, all patients ultimately develop tumor progression and castration resistance (65). The role of *TP53* inactivation in response to androgen deprivation therapy has not been studied in detail. Thus far, there appears to be no negative impact of *TP53* alterations in the response to first-line antihormonal treatment (52). In the last decade, several novel therapeutic options for patients with mCRPC have been established including the CYP17 inhibitor abiraterone and the androgen receptor antagonist enzalutamide (66, 67). Since not all men benefit from these next-generation antiandrogens, there is a clinical need for markers that indicate primary or acquired resistance to aid decision-making. Because mCRPC still critically depends on AR signaling (68), the constitutively active AR splice variant V7 (AR-V7) has been suggested as a crucial, albeit not exclusive, component of the resistance mechanisms to next-generation antiandrogens (69, 70). De Laere and colleagues could demonstrate that inactivation of *TP53* was associated with significantly shorter progression-free and overall survival of prostate cancer patients treated with abiraterone or enzalutamide (71). The poorest progression free survival was found in patients with a biallelic *TP53* inactivation. Of note, *TP53* mutations were the only marker independently associated with an unfavorable response to abiraterone and enzalutamide and, remarkably, outperformed genomic AR alterations and expression of AR splice variants (71). How p53 influences resistance to next-generation antiandrogens remains to be clarified. Interestingly, there is evidence to suggest that wild-type p53 may suppress AR activation (72–74).

The microtubule-stabilizing agent docetaxel is the only chemotherapy that has been shown to extend survival in patients with mCRPC (75, 76). The response of prostate cancer cells to docetaxel has been found to be compromised by mutant p53 (77). The clinical utility of *TP53* mutation status as a predictive marker for docetaxel treatment hence warrants further investigation.

Whether and to what extend *TP53* perturbations affect the response to the PARP inhibitor olaparib, which has recently been approved for patients with mCRPC and *BRCA1/2* mutations (16, 18), is currently unclear.

TP53 AND THE CLONAL EVOLUTION OF PROSTATE CANCER

Since a substantial proportion of primary prostate cancers harbor mutations in *TP53*, the question arises whether *TP53* inactivation may be a driver event for malignant progression. There is mounting evidence that this could be the case. *TP53* mutations have been reported as truncal aberrations in considerable proportions of metastatic prostate cancers (58, 78). Interestingly, a case study could demonstrate that a mutant *TP53* clone originating from a small, well-differentiated focus of primary prostate cancer was apparently the origin of metastatic spread with a 17-year lag period (79). However, *TP53* mutations have also been reported to be enriched in metastatic lesions and there are also examples of tumors in which *TP53* aberrations can be found exclusively in metastases (52, 80).

In conclusion, *TP53* mutations seem to be an early event in some prostate cancers while in others an enrichment in metastatic lesions can be found. In the future, increasingly sensitive detection methods such as single-cell sequencing hold the promise to even better define the molecular composition of primary and metastatic prostate cancer with respect to the *TP53* mutation status.

DOES p53 HAVE POTENTIAL AS A THERAPEUTIC TARGET AFTER ALL?

Given the high frequency of *TP53* inactivation in prostate cancer and in cancer in general, the question remains how this finding could be translated into a therapeutic vulnerability. p53 is notoriously difficult to target and numerous studies have used approaches such as gene therapy, inhibition of MDM2 or MDM4 interactions, synthetic lethal approaches, and others (81–85). It should not be forgotten that p53 has originally been discovered as a tumor antigen induced by chemical carcinogens (86). Hence, approaches to exploit mutant p53 as immunological target as well as the increased genomic instability of p53-defective cells through immune oncological interventions still appear promising. In this context, an exacerbation of the mutational burden may further enhance the therapeutic vulnerability of p53-deficient cells to promote responses to immune checkpoint inhibitors.

CONCLUSION

Inactivation of *TP53* has initially been described as a late event during malignant progression and associated mainly with mCRPC. There is now compelling evidence that mutated *TP53* can also be detected in primary prostate cancer, and, especially, in castration-naïve metastatic prostate cancer. Inactivation of *TP53* predicts an unfavorable patient outcome, early metastatic dissemination, and resistance to next-generation antiandrogens. Therefore, *TP53* perturbations have a strong potential as a marker to identify patients with a high risk for lethal disease outcome who could benefit from more intensified treatment.

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