Title

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Journal

The Oncologist, 26(4)

ISSN

1083-7159

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Publication Date

2021-04-01

DOI

10.1002/onco.13694

Peer reviewed

The Oncologist®

Brief Communications

Landscape of Cyclin Pathway Genomic Alterations Across 5,356 Prostate Cancers: Implications for Targeted Therapeutics

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

The cyclin pathway may confer resistance to standard treatments but also offer novel therapeutic opportunities in prostate cancer. Herein, we analyzed prostate cancer samples (majority metastatic) using comprehensive genomic profiling performed by next-generation sequencing (315 genes, >500× coverage) for alterations in activating and sensitizing cyclin genes (*CDK4* amplification, *CDK6* amplification, *CCND1*, *CCND2*, *CCND3*, *CDKN2B* [loss], *CDKN2A* [loss], *SMARCB1*), androgen receptor (*AR*) gene, and coalterations in genes leading to cyclin inhibitor therapeutic resistance (*RB1* and *CCNE1*). Overall, cyclin sensitizing pathway genomic abnormalities were found in 9.7% of the 5,356 tumors. Frequent alterations included *CCND1* amplification (4.2%) and *CDKN2A* and B loss (2.4% each). Alterations in possible resistance genes, *RB1* and *CCNE1*, were detected in 9.7% (up to 54.6% in neuroendocrine) and 1.2% of cases, respectively, whereas *AR* alterations were seen in 20.9% of tumors (~27.3% in anaplastic). Cyclin sensitizing alterations were also more frequently associated with concomitant *AR* alterations. ***The Oncologist*** 2021;26:e715–e718

Introduction

The cyclin pathway is crucial for cell cycle control. In cancer cells, deregulation can lead to uncontrolled cell division and progression. Preliminary data in prostate cancer suggest that the cyclin pathway plays an important role in the evolution to a castrate-resistant state and demonstrates interplay with androgen signaling [1, 2]. A prior report indicates that next-generation sequencing can be helpful in advanced prostate cancer, revealing alterations in genes from cyclin pathway [3]. Breast cancer is a hormone-dependent cancer for which different cyclin inhibitors have been successfully approved. Clinical trials with cyclin inhibitors are ongoing in prostate cancer [4], and, thus, characterization of the landscape of cyclin pathway genomic alterations is needed. Herein, we analyzed prostate cancer samples (mostly metastatic) using comprehensive genomic profiling performed by next-generation sequencing

Materials and Methods

We analyzed 5,356 anonymized patient prostate cancer samples (majority metastatic) at a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited laboratory (Foundation Medicine). The proportion of samples from primary and metastatic sites in patients with prostate cancer in the database is approximately 48% and 52%, respectively [5]. Approval for the Foundation Medicine cohort, including a waiver of informed consent and Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (Protocol No. 20152817). Tissue diagnoses were designated according to the pathology report and further verified by a pathologist. Comprehensive genomic profiling was performed on hybridization-captured, adaptor ligation-based libraries (315 genes, >500× coverage). We described alterations in cyclin pathway sensitizing genes (8 genes, including *CDK4* amplification, *CDK6* amplification, *CCND1*, *CCND2*, *CCND3*, *CDKN2B* [loss], *CDKN2A* [loss], and *SMARCB1*) and genes related to resistance to cyclin inhibition (*RB1* and *CCNE1*; supplemental online Table 1). Co-occurrence analysis was performed matching cyclin-pathway sensitizing genomic alterations with three different subsets of genomic alter-

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ations (resistance pathway [*RB1* and *CCNE1*], cyclin-related [*SMAD3*, *CDKN1A*, *CDKN1B*, *CDKN2C*], and androgen receptor [*AR*]). Statistical analysis was performed using GraphPad Prism, Python 2.7, and Anaconda V4 (*Anaconda Software Distribution*, Vers. 4–4.3.21; https://anaconda.com). Co-occurrence analysis was performing matching cyclin-pathway genomic alterations with three different subsets of genomic alterations (resistance pathway, cyclin-related, and *AR*).

Results and Discussion

Alterations in any cyclin pathway sensitizing genes were found in 9.7% of the 5,356 tumors analyzed (the majority adenocarcinoma acinar [n = 4,897]), which is lower compared with other solid tumor types [6]. The most frequent type of alteration observed in cyclin sensitizing genes was copy number variation, except for *SMARCB1* (single nucleotide change). Frequencies by gene were distributed according to Figure 1A. The most frequent alterations were *CCND1* amplification (4.2%) and *CDKN2A/CDKN2B* loss (2.4% each). Histology was also important in regard to frequency of alterations. Ductal adenocarcinomas and anaplastic tumors were enriched for cyclin sensitizing alterations, especially *CDKN2A/B* loss. Both genes were also frequently altered in tumors with a mesenchymal component (sarcomas and carcinosarcomas) despite the low number of samples.

Resistance to CDK inhibitors can be mediated by genomic alterations in genes such as *RB1* and *CCNE1* [7]. Overall, alterations in these genes were present in 9.7% and 1.2% of prostate cancer samples, respectively (Fig. 1B). Neuroendocrine tumors presented a high frequency of *RB1* alterations (54.6%). We also analyzed the likelihood of co-occurrence of a sensitizing alteration in the cyclin pathway and in a possible resistance pathway. A lower likelihood of co-occurrence compared with an isolated alteration in cyclin sensitizing and resistance pathway genes was demonstrated (odd ratio [OR], 0.44; $p < .001$; Fig. 2; supplemental online Table 2), which suggests potential feasibility for activity of cyclin inhibitors.

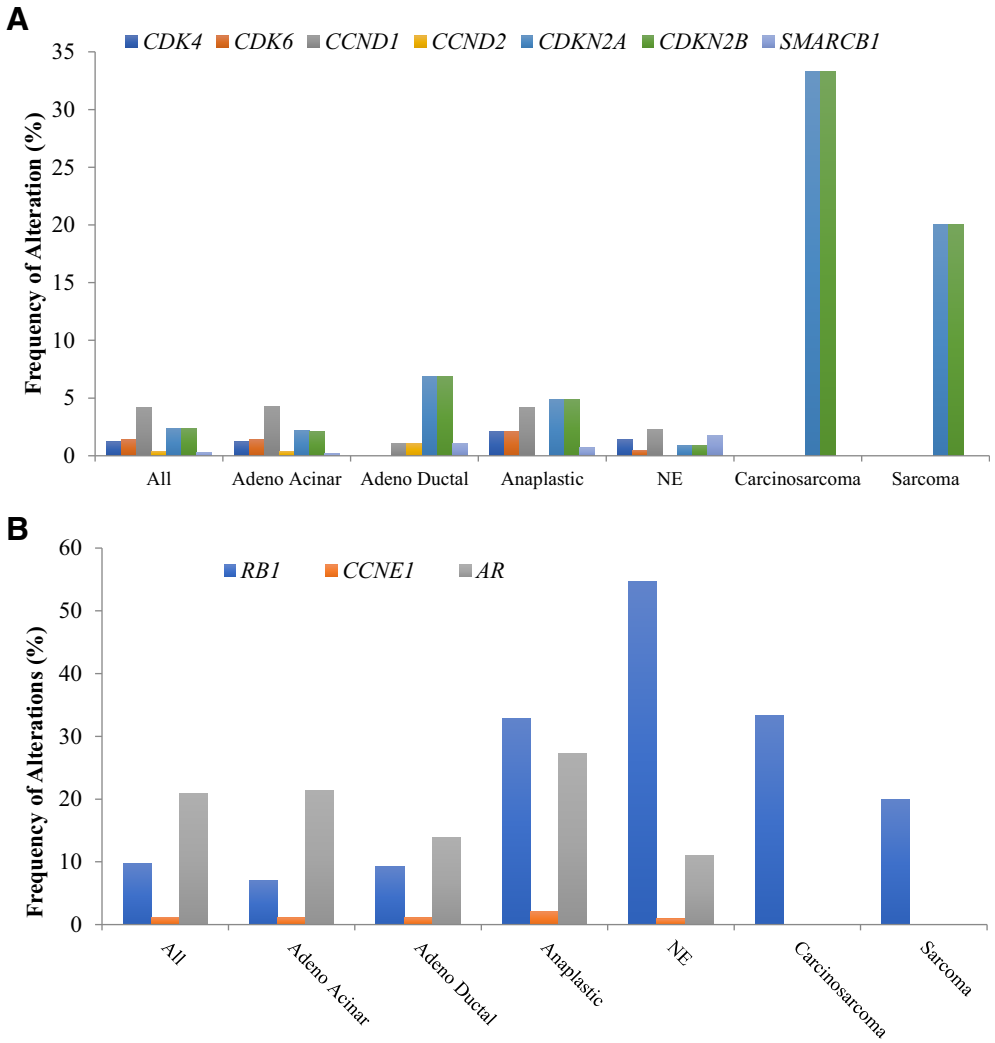

Figure 1. Frequency (percentage of patients) of each listed alteration in prostate cancer. **(A):** Cyclin pathway gene alterations in patients with prostate cancer alterations in **(B)**. Alterations in putative cyclin resistance genes (*RB1* and *CCNE1*) and *AR*
Abbreviations: adeno, adenocarcinoma; *AR*, androgen receptor; NE, neuroendocrine.

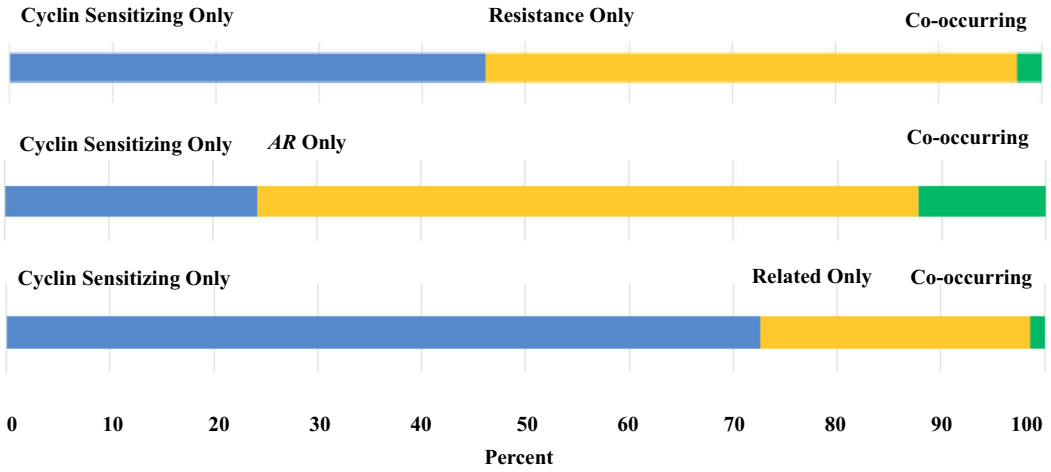

Figure 2. Co-occurrence analysis of cyclin sensitizing (*CDK4*, *CDK6*, *CCND1*, *CCND2*, *CCND3*, *CDKN2B, CDKN2A*, and *SMARCB1*) and resistance genes (*RB1* and *CCNE1*), *AR*, and cyclin-related genes (*SMAD3*, *CDKN1A*, *CDKN1B*, *CDKN2C*). Percent refers to percentage of patients with an alteration. Patients with neither alteration are not included in this graphic, but the numbers are given in supplemental online Table 3.
Abbreviations: *AR*, androgen receptor.

AR gene alterations can also occur in advanced prostate disease. In fact, 20.9% of all samples had *AR* alterations, with higher frequency in anaplastic tumors (27.3%). Overall, this frequency is lower compared with other genomic sequencing series, which described alterations in *AR* in approximately 60% of patients [8–10]. However, these prior series included only metastatic castration-resistant prostate cancer, a state enriched for *AR* abnormalities. Our series included both primary and metastatic disease and was not restricted to castrate-resistant advanced disease. Co-occurrence analysis demonstrated a significant co-occurrence between *AR* and sensitizing cyclin alterations (as compared with *AR* alterations in patients wild type for sensitizing cyclin alterations; OR, 1.79; $p < .001$; Fig. 2; supplemental online Table 2). In prostate cancer, the cyclin pathway may interplay with androgen signaling but may also mediate AR independence [11, 12]. A positive co-occurrence of *AR* and cyclin sensitizing gene alterations might suggest the existence of a subset of patients with more intense resistance to monotherapy with next-generation antiandrogens that could be addressed with cell cycle inhibitors as part of the therapeutic strategy. Interestingly, preclinical rationale suggests further testing of CDK4/6 inhibitors in this setting [13].

It is important to put our data from 5,356 patients with prostate cancer in perspective with other publications interrogating smaller numbers of patients (supplemental online Table 3). The Cancer Genome Atlas Program (available at http://www.cbioportal.org) included data from 494 prostate cancer samples (predominantly primary tumors) and described a lower frequency of cyclin sensitizing alterations. Other series with a mixture of primary and metastatic samples revealed frequencies that are more similar to our results (n = 1,013 samples analyzed) [14]. Taken together, we can hypothesize that cyclin sensitizing alterations are enriched in advanced tumors, perhaps as a result of therapeutic pressure or accumulation of genetic alterations during the course of disease. This study has several limitations, including the lack of clinical correlates, which limits possible associations of genomic alteration with prognosis and response to therapies in prostate cancer. These data support cyclin pathway alterations as relevant for the progression of prostate cancer and may inform opportunities for targeted therapy, especially for cyclin inhibitors alone or in combination with antiandrogens.

Acknowledgments

Funded in part by National Cancer Institute grant P30 CA016672 and the Joan and Irwin Jacobs Fund philanthropic fund (all funds received by Razelle Kurzrock).

Disclosures

Denis L. Jardim: Roche, Janssen, Astellas, Merck Sharpy & Dohme, Bristol-Myers Squibb, Libbs (Speaker fees), Janssen, Bristol-Myers Squibb, Libbs (C/A); **Sherri Millis:** Foundation Medicine (E); **Jeffrey Ross:** Foundation Medicine (E); **Michele Sue-Ann Woo:** Daiichi Sankyo, Foundation Medicine (E); **Siraj M. Ali:** EQRx Inc (E, equity), Foundation Medicine (E), In8bio, Elevation Oncology, Pillar Biosciences (SAB), Takeda, ArcherDX (C/A); **Razelle Kurzrock:** Genentech, Merck Serono, Pfizer, Boehringer Ingelheim, TopAlliance, Takeda, Incyte, Debiopharm, Medimmune, Sequenom, Foundation Medicine, Konica Minolta, Grifols, Omniseq, Guardant (RF), X-Biotech, Neomed, Pfizer, Actuate Therapeutics, Roche, Turning Point Therapeutics, TD2/Volastra, Bicara Therapeutics, Inc., (C/A, Speaker fees), IDbyDNA and CureMatch Inc (Equity interest), CureMatch and CureMetrix (Board member), CureMatch (Cofounder).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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See http://www.TheOncologist.com for supplemental material available online.