IN THE SPOTLIGHT

Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression?
Joanna Triscott¹ and Mark A. Rubin¹,²

Summary: PI3K pathway alterations are frequently recurrent in metastatic prostate cancer and are associated with the development of currently incurable castration-resistant disease. Candidate inhibitors that target single PI3K pathway members lack efficacy as demonstrated in multiple clinical trials. In this issue, Pearson and colleagues examine the functional importance of co-occurring Pik3ca and Pten aberrations using a novel mouse model and demonstrate a synergistic acceleration of tumorigenesis that may be responsible for de novo metastatic prostate cancer.

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See related article by Pearson et al., p. 764 (6).

Second only to lung cancer, advanced prostate cancer is a major cause of cancer-related death in men. A dire need exists to develop a better understanding of how progression to advanced castration-resistant prostate cancer (CRPC) occurs. The dominant mechanism of resistance for targeted androgen receptor (AR)-based therapy is reactivation of AR signaling. However, hyperactivation of other key cancer-promoting signaling pathways has been suggested to accelerate the onset of hormone resistance to early-stage, or de novo, CRPC (1).

Large-scale collaborative efforts in the field have identified the PI3K–AKT signaling axis to be the most frequently altered pathway in advanced prostate cancer (2). PI3K is a lipid kinase made up of a regulatory and catalytic heterodimer that can be paired using different protein isoform combinations. Catalytic subunits are encoded by Pik3ca (p110α), Pik3cb (p110β), and Pik3cd (p110δ; Fig. 1A). PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PiP2) to phosphatidylinositol (3,4,5)-trisphosphate (PiP3), and this results in the downstream activation of the protein kinase AKT. This subsequently activates mTORC1 and mTORC2, which are implicated in directing cell proliferation, migration, and cell survival. Pten is an established tumor suppressor that is responsible for containing PI3K activity by converting PiP3 back into PiP2. Heterozygous or homozygous loss of PTEN occurs in roughly two fifths of patients with metastatic prostate cancer (2). Recently, the characterization of 1,013 tumor and matched germline prostate cancers detected PI3K pathway genomic alteration in 17% of primary tumors, and these were further enriched in 40% of cases with metastatic disease (1). Although genomic studies identify candidate drivers of CRPC progression, the functional characterization of these genetic changes is an enormous undertaking. Genetically engineered mouse (GEM) models that allow tissue-specific deletion of a gene of interest have become a mainstay in the field, especially the PbclCre⁰/⁰ model that expresses androgen-stimulated Cre recombinase following puberty to homoeozously delete Pten in prostate epithelium (3). The mouse model of Pten loss has been used to examine the functional importance of multiple key factors that drive prostate cancer, including MYC, SOX2, TP53, KRAS, BRAF, SMAD4, TERT, and recently SPOP (4, 5).

In this issue of Cancer Discovery, Pearson and colleagues utilize the PbclCre⁰ system to functionally explore the biological impact of the Pik3caH1047R (Pik3caHR)-activating mutation in the prostate and further explore if this aberration cooperates with Pten deletion to accelerate the progression of prostate cancer to CRPC (6). The motivation to develop this new prostate-specific Pik3ca model stems from initial observations in multiple prostate cancer genomic datasets. Examination of nine patient cohorts identified Pik3ca mutations and amplifications that have previously been suggested to increase p110α kinase activity. This gain of function is significantly correlated to attributes of poor patient outcome such as lymph node metastasis, Gleason grade, and recurrence-free survival. Importantly, around 45% of patients with Pik3ca mutation or amplification/gain also harbored mutation or loss of Pten. What would drive apparently redundant genomic alterations? Pearson and colleagues addressed the following three questions: (i) What is the oncogenic role of Pik3caH1047R mutation in the prostate? (ii) Are there phenotypic differences between mutant Pik3ca and Pten-null tumorigenesis? (iii) If non-redundant, do Pik3ca and Pten aberration cooperate to produce CRPC?

The authors generated a PbclCre⁰/Pik3caH1047R (referred to as Pik3caHR) mouse mutant of prostate-specific, heterozygous p110α activation. Histologic characterization of individual prostate lobes over the duration of 400 days showed that Pik3caHR mutation stimulated a progressive malignant

¹Department of BioMedical Research, University of Bern, Bern, Switzerland.
²Weill Cornell Medical College, New York, New York.

Corresponding Author: Mark A. Rubin, Department of BioMedical Research, University of Bern, Murtenstrasse 35, MEM H621, 3008, Bern, Switzerland. Phone: 41-31-632-98-65; Fax: 41-31-632-09-46; E-mail: mark.rubin@dbmr.unibe.ch
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phenotype that developed from mild hyperplasia (day 56) to locally invasive prostate carcinoma (days 300–400). This is the first in vivo evidence to confirm that single-allele Pik3caHR mutation is sufficient to induce prostate cancer in mice (6).

Next, Pearson and colleagues considered the Pik3caHHR mutant phenotype relative to the established PBiCre+/−;Ptenfl/fl (referred to as Pten+) model as both alterations activate the PI3K pathway. They found the Pten+ animals had earlier onset of hyperplasia and a more rapid progression to invasive carcinoma, as well as greater tumor burden and significantly more proliferating cells compared with Pik3caHHR hyperplastic tissues, and higher expression of the cytokeratin-8 marker of basal cell lineage. These data show that the Pik3caHHR single mutant is an activating mutation that promotes murine cancer progression and—although comparable to the Pten-null model—there are distinct phenotypic differences that suggest that these key PI3K pathway components do not phenocopy. Understanding these differences may reveal unique functions of Pik3ca and Pten that may offer novel therapeutic opportunities.

Stemming from the initial animal model development, the authors questioned if Pik3ca and Pten loss models parallel in downstream molecular signaling. Using immunohistochemistry (IHC), both models showed activation of the AKT–mTORC signaling, and, together appear to synergize. Histologic characterization of the GEM models demonstrates differences in onset of hyperplasia and progression to invasive prostate carcinoma. A summary of the molecular findings of this is shown. 

Figure 1. Graphical abstract summary of Pearson et al. (6). A, Class I PI3K is composed of a regulatory and catalytic subdomain coded for by any of the PIK3CA, PIK3CB, or PIK3CD genes. PI3K activity converts PIP2 to PIP3 and is reversed by PTEN. AKT and mTORC signaling are substrates of PI3K pathway activation promoting downstream modulation of cell proliferation, growth, survival, and migration. GEM models can alter this pathway specifically in prostate tissue using PBiCre expression and a Ptenfl/fl allele and/or Pik3caHR activating mutant of the p110α catalytic subunit. Pik3caHR and Pten deletion both function to activate PI3K–AKT–mTORC signaling, and together appear to synergize. B, Histologic characterization of the GEM models demonstrates differences in onset of hyperplasia and progression to invasive prostate carcinoma. A summary of the molecular findings of this is shown.
identifying another nonredundant phenotype whereby Pten-deleted tumors may preferentially drive malignancy via p110β activation (6).

Credentiaing the importance of PI3K catalytic subunit dependency (p110α or p110β) has therapeutic implications given the active development of drug inhibitors in this class, many of which are being tested in clinical trials. Pan-PI3K inhibitors, such as BKM120 and BYL719, are being tested for treatment of breast, colon, ovarian, and more recently metastatic prostate cancers (clinical trial NCT012196999). Pearson and colleagues directly explore p110α and p110β dependency of the Ptenfl/fl and Pik3caH1047R models using BKM120, A44 (p110α-specific inhibitor), and TGX-221 (p110β-specific inhibitor) treatment on mice that were stage-matched for prostate carcinoma. Pik3caH1047R tumor burden regressed with A66 and BKM120, suggesting p110α dependency for this driver mutation, whereas Ptenfl/fl is thought to be p110α/p110β codependent, as tumor regression was observed only with pan-inhibition of both isoforms. These data are well aligned with previous work that shows PI3K isoform-specific mono-therapies are ineffective for the treatment of PTEN-null prostate cancer (7).

After discovering that PIK3CA mutation and PTEN loss can co-occur in patients, the investigators developed a PbCre; Pik3caH1047R.Ptenfl/fl (referred to as Pik3caH1047R.Ptenfl/fl) double-mutant mouse model. Combination of prostate-specific Pik3ca-activating mutation and Pten loss showed 100% incidence of invasive carcinoma with significantly greater tumor burden relative to age-matched single mutants (Fig. 1B). Double-mutant tumors had elevated IHC staining for PCNA-burden relative to age-matched single mutants (6). This model convincingly highlights the likelihood that alternative molecular functions of these factors are influencing cancer development. This is exemplified by recent work revealing novel substrates of PTEN in addition to PIP3 (9). As well, the field has yet to determine the biological impact of the lesser-known type 2 phosphatidylinositol-5-phosphate 4-kinase network, and the extent to which it may influence efficacy of PI3K-AKT-mTOR targeted therapies in prostate cancer (10).

In summary, this work by Pearson and colleagues reports that the PIK3CAH1047R mutation is sufficient to produce locally invasive prostate cancer in vivo that is accelerated in combination with Pten loss. Although many genomic events accumulate with progression to CRPC, PIK3CA alteration offers an actionable target that ideally can be used to inform the individualization of patient treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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