Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression?

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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. Cancer Discov; 8(6):682–5. ©2018 AACR

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 countering 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 countering PI3K–AKT 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).

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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 \( \text{Pik3ca}^{+/\text{HR}} \) mutation is sufficient to induce prostate cancer in mice (6).

Next, Pearson and colleagues considered the \( \text{Pik3ca}^{+/\text{HR}} \) mutant phenotype relative to the established \( \text{PBiCre}^{++/\text{HR}};\text{Pten}^{fl/fl} \) model (referred to as \( \text{Pten}^{fl/fl} \)) as both alterations activate the PI3K pathway promoting downstream modulation of cell proliferation, growth, survival, and migration. GEM models can alter this pathway specifically in murine prostate tissue. Using \( \text{PBiCre}^{++/\text{HR}};\text{Pten}^{fl/fl} \) and \( \text{Pik3ca}^{+/\text{HR}} \) deletion both function to activate PI3K–AKT–mTORC signaling, and together appear to synergize.

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).

Credentialing 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 BKM210 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 Pik3cafl/fl models using BKM120, A44 (p110α-specific inhibitor), and TGX-221 (p110β-specific inhibitor) treatment on mice that were stage-matched for prostate carcinoma. Pik3cafl/fl 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 that PI3K isoform-specific mono-therapies are ineffective for the treatment of Pten-null prostate cancer (7).

After discovering that PI3CA mutation and PTEN loss can co-occur in patients, the investigators developed a Pik3cafl/fl, Pik3cafl/fl, Ptenfl/fl (referred to as Pik3cafl/fl, 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 demonstrates that Pten deletion together with Pik3ca mutation can synergistically accelerate cancer progression, and do so by cooperatively increasing proliferative mechanisms without rewiring survival pathways.

Clinically, loss of PTEN is associated with resistance to androgen deprivation therapy (7, 8). The authors therefore sought to determine if Pik3cafl/fl mutation can confer castration resistance in mice. Surgical castration of Pik3cafl/fl and Ptenfl/fl mice reduced prostate tumor volume compared with noncastrates but did not entirely eliminate tumors due to the acquired development of CRPC. In contrast, castration of Pik3cafl/fl, Ptenfl/fl double mutants did not significantly alter tumor burden relative to noncastrates controls. Double-mutant tumors showed no change in already-elevated markers of cell proliferation and displayed attributes of CRPC (i.e., androgen receptor nuclear localization) earlier than the single-mutant models of acquired resistance. There was also hyperactivation of mTORC1 and AKT, which was maintained following castration of the double mutant. Taken together, these observations reflect the properties of de novo CRPC that is nonresponsive to androgen ablation from the early or beginning stages.

Finally, Pearson and colleagues delve into the potential mechanisms responsible for promoting the synergy between Pik3ca-mutant and Pten-deleted CRPC using a reverse-phase protein array (RPPA). Distinct signaling events were identified between Pik3cafl/fl and Ptenfl/fl tumors that involve the PI3K cascade, MAPK, and tyrosine kinase–mediated signaling. Although the single-mutant samples showed RPPA profile differences between castrated and uncastrated tumors, the double-mutant mice had little variation between castrated and controls. Providing further insight, the authors nominate NDRG inactivation as a potential mechanism of de novo CRPC, as increased phospho-NDRG1—a substrate of the mTORC2 pathway—is detected in post-castrated Pik3cafl/fl, Ptenfl/fl mice. These data highlight the existence of distinct signaling functions of Pik3ca mutation and Pten loss that contribute to the progression of prostate cancer and suggest novel cooperative mechanisms that drive castrate-resistant disease.

The phenotypic nonredundancy of Ptenfl/fl and Pik3cafl/fl models 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 PIK3CAfl/flH1047R 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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