Interrogating how *PIK3CA* oncogenic mutation contributes to prostate cancer

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Background: Prostate cancer is the second major cause of cancer related deaths in men globally, reflecting resistance to standard clinical regimens(1). Thus, there is an urgent need to identify new therapeutic approaches to improve our management of this disease. PI3K signalling regulates AKT/mTOR signalling to mediate cell growth/survival/migration and is invariably activated in advanced prostate cancer, thus presenting an attractive therapeutic target(2-5). Although genetic alterations that cause oncogenic PI3K signalling are common in prostate cancer, how distinct genetic drivers of the PI3K pathway facilitate prostate cancer is unclear. We sought to determine the mode of action of a poorly characterised driver of the PI3K cascade, namely *PIK3CA* oncogenic mutation.

Methods: To gain a better understanding of the frequency and predictive value of *PIK3CA* genetic aberrations in prostate cancer, we interrogated publicly available genomic datasets via cBioPortal/TCGA. To determine if *Pik3ca* mutation causes prostate tumorigenesis *in vivo*, we employed a conditional transgenic approach to mutate *Pik3ca* in murine prostate epithelium and characterized the prostate phenotype relative to PTEN-depleted prostate tumors using quantitative real-time PCR, immunohistochemistry, in situ hybridization and a reverse-phase protein array (RPPA)(6).

Results: We show *PIK3CA* genetic alterations correlate with poor prostate cancer prognosis and that *Pik3ca* oncogenic mutation at H1047R (a clinically relevant hotspot) predisposes to p110α-dependent invasive prostate carcinoma *in vivo*, which does not phenocopy PTEN loss. We report that *PIK3CA* mutation and *PTEN* loss co-exist in prostate cancer, and can cooperate to accelerate disease progression via AKT-mTORC1/2 hyperactivation. Furthermore, while single mutants were observed to slowly acquire castration-resistant prostate cancer (CRPC), *Pik3ca* mutation and *Pten* loss synergized to drive *de novo* CRPC. Thus, *Pik3ca* mutation and PTEN loss are not functionally redundant and accordingly display distinct RPPA profiles.

Conclusions: Our findings indicate that *PIK3CA* mutation is an attractive prognostic indicator for prostate cancer that may cooperate with *PTEN* loss to facilitate CRPC in patients. Establishing the molecular events that underpin this synergistic relationship may present new therapeutic/prognostic approaches to overcome CRPC and resistance to PI3K pathway inhibition.

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