A reciprocal feedback between the PDZ-binding kinase and androgen receptor drives prostate cancer

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Background
Aggressive prostate cancer (PrCa) becomes resistant to the androgen deprivation therapy (ADT) and is often fatal. Activation of the androgen receptor (AR) signalling despite ADT is an important feature of tumours known as castration resistant prostate cancer (CRPC) for which therapeutic options are limited. Androgens are main driver of PrCa that manifest their action via activation of the AR signalling. Androgens can also negatively regulate AR mRNA expression by recruitment of AR to AR gene. Despite decreasing AR mRNA levels, androgens promote AR stabilisation leading to overall increase in AR protein expression. This highlights the critical need to analyse the androgen-regulated proteome in order to characterise androgen-regulated changes at protein level in PrCa. In order to understand how AR is stabilised and promotes PrCa growth, it is imperative to identify clinically relevant AR targets, both up- and downstream of AR signalling.

Methods
To understand the mechanism by which AR is activated and to understand its downstream signaling in CRPC, we employed Proteomics based approaches. Transcriptomic profiling approaches were used to identify molecular pathways that are altered in CRPC. Further we employed biochemical and functional assays to understand the biological basis of resistant. The level of expression of the identified factor was assessed in clinical samples using series of prostate cancer tissue that represent CRPC.

Results and conclusions
Androgen-regulated proteome identified PDZ binding kinase (PBK) as a key effector of androgen signalling that integrates AR signalling with PrCa growth. In men with PrCa, PBK is androgen-regulated and localised in the tumour cell nucleus. PBK overexpression is associated with poor disease outcome and clinical progression. We further uncover PBK interactome and identify a crucial reciprocal feedback between PBK and AR, whereby PBK interacts with both the NTD and LBD of AR to directly regulate the stability and function of both full-length AR and ARVs. Inhibition of PBK activity destabilises AR and decreases PrCa growth and metastasis. These results provide novel insights into

the role of androgen-induced pathways in PrCa revealing PBK as a key effector through which AR manifest its oncogenic function in PrCa.
Therapeutically targeting of PBK is a novel and attractive treatment approach for the otherwise fatal CRPC. Small peptides-based medicinal chemistry approaches to disrupt PBK:AR interaction will be suited to develop precise targeting approaches to effectively inhibit AR activation in CRPC.

Conflict of Interest

Authors declare that there is no conflict of interest.

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