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Role of Wnt Signalling in Advanced Prostate Cancer

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Abstract

Recent next-generation-sequencing studies demonstrate that multiple pathways are often deregulated in advanced and metastatic prostate cancer (PC). In a recent issue of The Journal of Pathology, an elegant study by Jefferies et al used in vivo modelling to demonstrate how activation of the PI3K, WNT and MAPK pathway converges on mTORC1 signalling to drive aggressive disease. The study also highlights that approaches to target advanced PC require intelligent combination of agents to target single/multiple signalling pathways in combination with androgen receptor (AR) blockade.
In a recent issue of the Journal of Pathology, Jefferies et al [1] investigated the impact of deregulated MAPK and WNT pathway activation, on a background of PTEN loss in a compound murine model of prostate cancer (PC). The murine Probasin (Pb) Cre-LoxP model of PC, driven by Pten (Pten$^{fl/fl}$) loss is one of the most widely studied models of this disease process in vivo [2]. This model however is slow growing, with tumour latency approaching 12 months and rarely metastasises without co-operating mutations [3].

Using both tissue microarrays and in silico analyses Jefferies et al demonstrated that concurrent WNT, PI3K, and MAPK pathway was associated with advanced PC, correlating with p-S6 kinase expression, a downstream marker of the mTORC1 pathway [1] (Figure 1). To model this in vivo, they next went on generate a genetic model with activation of all three pathways (Catnb$^{-/-}\text{lox(ex3)}$Pten$^{fl/fl}$K-Ras$^{+/V12}$). This model had significantly earlier morbidity and mortality (median survival 96 days) compared to the single and double mutants [1]. Interestingly a proportion of the double mutants (10% of Catnb$^{-/-}\text{lox(ex3)}$Pten$^{fl/fl}$ and 60% of Pten$^{fl/fl}$K-Ras$^{+/V12}$) demonstrated retroperitoneal lymph node metastasis, whilst the triple mutants did not display any evidence of metastatic disease, presumably due to the rapid progression of the primary tumour in this model [1].

The triple mutant mice demonstrated activation of WNT (nuclear β-catenin), PI3K (pAKT$^{Thr308}$) and focal MAPK staining (p-ERK1/2). The ribosomal protein S6 (p-S6$^{240-244}$), a marker of mTORC1 pathway activation, was only significantly elevated in the triple mutants versus the double mutants, suggesting suppression of negative feedback loops controlling mTORC1 in the double mutants [1].

In humans, inhibitors of the mTOR pathway, such as rapamycin or everolimus, have demonstrated minimal effect in Phase I/II clinical trials on either Prostate Specific
Antigen (PSA) levels or clinical progression when used as single agents [4, 5]. This intrinsic resistant to mTORC1 inhibitors has been suggested to be due to MAPK activation through a PI3K-dependent feedback loop [6], and as reviewed by Jefferies et al multiple preclinical studies have demonstrated the promise of combined PI3K/mTOR inhibition [1].

This study also reinforces the important role that WNT signalling plays in PC. Recent next-generation-sequencing (NGS) studies of WNT signalling in PC have shown that APC is one of the most significantly mutated genes in lethal and heavily treated tumours [7]. Sequencing of bone or soft tissue metastasis from 150 patients with castrate resistant PC (CRPC) demonstrated mutation of the WNT signalling pathway in 18% of cases [8]. The WNT cascade can act as a master regulator by integrating signals from PI3K/mTOR, MAPK and AR pathways:

- WNT-dependent inhibition of GSK-3β to stimulate mTORC1 via TSC1/2 axis [9]
- Transcription of AR through TCF/LEF1 (Reviewed in [10])
- c-Myc transcription and activation of MAPK signalling [11]
- Inhibition of MAPK driven senescence [12]

Therefore, WNT signalling has become an attractive pathway to target in CRPC, particularly given its role in advanced disease, where multiple pathways are active concurrently. Although a variety of agents exist, from monoclonal antibodies to small molecule inhibitors, few have made it to clinical trials [13, 14].

The study by Jefferies et al highlights how advanced PC is driven by numerous pathways, often with different levels of regulation and multiple feedback loops [1]. NGS of patient’s primary prostate tumours and metastasis provides the opportunity to identify which pathways are likely to be activated in both treatment naive and pre-
treated lesions, allows patients to be commenced on appropriate therapies, whether it be with PI3K, WNT and/or MAPK inhibitors in combination with AR inhibition.

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**Figure 1:** Interaction of PI3K, MAPK and WNT signalling pathways drives PC through mTORC1 signalling