THEMATIC REVIEW

Advances in preclinical models of prostate cancer for research discovery

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Abstract

There is longstanding interest in the role of androgens in the aetiology of prostate cancer, one of the most common malignancies worldwide. In this review, we reflect on the ways that knowledge of prostate development and hormone action have catalysed advances in the management of patients with prostate cancer. The use of hormone therapies to treat prostate cancer has changed significantly over time, including the emergence of androgen receptor signalling inhibitors (ARSI). These compounds have improved outcomes for patients with castration-resistant prostate cancer, which was once considered ‘androgen-independent’ but is clearly still driven by androgen receptor signalling in many cases. There is also a need for new therapies to manage neuroendocrine prostate cancer, which is not responsive to hormonal agents. One of the major gaps is understanding how treatment-induced neuroendocrine prostate cancer emerges and whether it can be re-sensitised to treatment. Patient-derived models, including patient-derived xenografts (PDXs), will be instrumental in facilitating future discoveries in these areas. Developments in the use of PDXs have been fostered by lessons from the field of endocrinology, such as the role of stroma and hormones in normal and developmental tissues. Thus, there is ongoing reciprocity between the discoveries in endocrinology and advances in prostate cancer research and treatment.

Introduction

The prostate gland is a hormonally regulated organ that commonly becomes bothersome with age. Benign prostatic hyperplasia and prostate cancer have different aetiologies, but both have an inestimable impact on patients and their families. Despite many new treatments that extend survival, advanced prostate cancer remains incurable.

Key Words

- prostate cancer
- patient-derived xenograft
- organoid
- pathology
- preclinical testing

Over decades, urologists, anatomists and biologists have sought to understand the anatomy, physiology and pathologies of the prostate gland during development, in health and in disease. As trainees and members of the endocrine societies, we focussed on the mechanisms of action of hormones (androgens and estrogens) on this gland following the seminal work of Huggins on
the effects of castration on the prostate (Huggins 1942). Cloning of the androgen receptor (AR) was a pivotal step in understanding the role of androgens (Lubahn et al. 1988, Tilley et al. 1989). It was complemented by studies into the effects of other nuclear receptors on prostate function, including estrogen receptor 1 (ERα) and estrogen receptor 2 (ERβ) (Risbridger et al. 2001a,b, Cunha et al. 2004). Sessions at endocrine conferences and other specialist meetings were devoted to understanding hormone action and development of the prostate gland in the belief that normal developmental regulatory mechanisms go awry in benign and malignant disease.

Discovery of the role of hormones in maintaining prostate homeostasis was translated into several changes in clinical practice, including the emergence of treatments for benign prostate hyperplasia. This includes the use of finasteride to block 5α reductase conversion of testosterone to the more potent 5α dihydrotestosterone. For more than 70 years, the treatment of advanced prostate cancer has been based on blockade of androgen action, such as through castration. There have been significant changes in how androgen deprivation therapy (ADT), as it is now known, is administered. Yet, blockade of androgens alone is not sufficient to cure prostate cancer, and even when ADT is combined with other therapies, tumours still develop resistance (Risbridger et al. 2022).

It is consideration of this last point, from which we begin our review. Our summary of the current clinical landscape of prostate cancer reveals the need for newer models for preclinical evaluations. This is where we have made significant advances beyond the use of immortalised cell lines collected from patients several decades ago, long before the introduction of many therapies used as standard of care. Although we mainly use patient-derived xenografts (PDXs), they are commonly used together with organoids as research tools for discovery, target validation and therapy evaluation.

**The current clinical landscape of prostate cancer**

In the decades since Huggins introduced the concept of ADT, the range of treatment options for prostate cancer has expanded considerably, but there are still echoes of the clinical challenges from the 1940s. Each year, approximately 1,400,000 people globally are diagnosed with prostate cancer, and 375,000 die due to the disease (Sung et al. 2021). Most patients have adenocarcinoma, where the tumour cells express markers of luminal prostate epithelial cells, including the AR and prostate specific antigen (PSA). The morphology of tumour foci is categorised into Gleason grade groups to estimate the risk of disease progression (Epstein et al. 2016). Additional growth patterns of prostate adenocarcinoma can be used to refine risk stratification, including ductal morphology (which is included in the Gleason grading) and intraductal carcinoma of the prostate (IDC-P, which is reported separately from Gleason grade groups) (Lawrence et al. 2020).

Rarely, patients are diagnosed with neuroendocrine prostate cancer (NEPC), which lacks AR and PSA expression, and expression of one or more markers of the neuroendocrine lineage, including chromogranin A, synaptophysin, neuron-specific enolase, chromogranin A (CHGA), synaptophysin (SYP), enolse 2 (neuron-specific enolase;NSE) and neural cell adhesion molecule 1 (CD56). NEPC is typically aggressive and associated with shorter survival (Aggarwal et al. 2014). Since NEPC lacks the AR, it is inherently resistant to AR-directed therapies, and thus, patients receive platinum-based chemotherapies instead (Nakabayashi et al. 2008, Humeniuk et al. 2018). In addition to patients with pure NEPC, up to 41% of adenocarcinoma specimens also stain with the most common neuroendocrine marker, chromogranin A (Kannan et al. 2022). Known as adenocarcinoma with neuroendocrine differentiation, there is significant variation in reporting and neuroendocrine foci or discrete staining is not routinely recorded in pathology reports.

For patients diagnosed with localised prostate cancer, curative treatments include surgery and radiation therapy (Fig. 1). Low-risk disease can be managed with active surveillance, with periodic imaging and biopsies to monitor disease progression and avoid or delay the side effects of treatment. Patients who have metastases at the time or diagnosis or who develop recurrent prostate cancer after local treatments usually receive systemic treatments.

ADT remains the backbone of treatments for metastatic prostate cancer (Fig. 1). It can be administered alone or in combination with either docetaxel (a taxane chemotherapy) or AR signalling inhibitors (ARSI) (Sweeney et al. 2015, James et al. 2016, Armstrong et al. 2019, Chi et al. 2019, Davis et al. 2019, Fizazi et al. 2019). In addition, recent trials show that triplet therapy with ADT, docetaxel and ARSI extends patient survival (Fizazi et al. 2020, 2022). Regardless of whether patients receive ADT alone or as a combination therapy, most eventually develop castration-resistant prostate cancer (CRPC) (Scher et al. 2004). It is evident from the Kaplan–Meier curves from clinical trials that there is wide variation in how long it takes for patients to develop CRPC. For example, approximately 10% of patients receiving triplet therapy...
with ADT, docetaxel and darolutamide developed CRPC within a year, but approximately 60% did not progress to CRPC after more than 4 years (Smith et al. 2022). This highlights several ongoing challenges in managing patients with advanced prostate cancer, including (1) the need for biomarkers to predict which tumours will rapidly fail treatment, (2) management of side-effects for patients on long-term androgen deprivation and (3) the importance of subsequent lines of treatment for patients once they develop CRPC.

The AR remains a therapeutic target in most cases of CRPC, so patients are usually treated with ARSI, particularly if they have not already received an ARSI in combination with ADT. In some patients, however, the selective pressure of sustained suppression of AR signalling leads to transformation of tumours into AR-negative and neuroendocrine phenotypes, which are inherently resistant to ARSI (Beltran et al. 2019). Treatment-induced NEPC is increasing in frequency, presenting an emerging clinical challenge (Bluemn et al. 2017). Patients may also receive taxane chemotherapy with docetaxel or cabazitaxel. Molecularly targeted therapies are also available for some patients, including PARP inhibitors (olaparib or rucaparib) for tumours with genomic defects in DNA damage repair genes (Abida et al. 2020, de Bono et al. 2020). Recently, the FDA also approved \(^{177}\)Lu-PSMA-617, a radioligand therapy for tumours with robust PSMA expression (Hofman et al. 2021, Sartor et al. 2021). Despite this growing range of treatments, advanced prostate cancer remains incurable as tumours develop diverse mechanisms of drug resistance. Therefore, there is an ongoing need for preclinical and clinical development of new treatments for the heterogeneous AR-positive and AR-negative phenotypes of advanced prostate cancer.

**Variations in the clinical landscape of prostate cancer**

With the increasing number of therapies for advanced prostate cancer, patients will receive different patterns of care. This is based on many factors, such as patient choice;
health status and co-morbidities; the features of the tumour, including pathology, genomic alterations, and the number and location of metastases, and access to care. In addition, some new treatments require sophisticated infrastructure to screen and treat patients. For example, genome-sequencing equipment is required to detect alterations in DNA damage repair genes for patients to receive PARP inhibitors, and radio-pharmacy facilities are required to produce radioligands for $^{177}$Lu-PSMA-617. In countries without extensive healthcare infrastructure, a more modest variety of treatments are available for prostate cancer. The World Health Organisation Model List of Essential Medicines includes several treatments for prostate cancer among the complementary list of compounds for priority diseases (Table 1) (WHO 2021). Enzalutamide is the most recent addition to the list, included as an alternative to abiraterone.

**Patient-derived prostate cancer models**

When a patient is diagnosed with prostate cancer, clinicians evaluate the clinical, pathological and imaging-based features of the tumour to determine the standard of care appropriate for the stage of disease. Clinical management varies considerably depending on the stage of progression and type of tumour present in each patient. Every effort is made to deliver optimal treatment to each patient. However, the precision with which clinicians seek to treat patients is not always replicated in the way that scientists simulate patient treatment in research. Only a limited range of prostate cancer models are widely available, often necessitating the use of models that inadequately represent the clinical challenge being studied. Preclinical studies might have greater predictive accuracy if they use models that represent different stages of disease progression and subtypes of pathology. Although cell lines have remained tools of choice for decades, the small number of widely used immortalised prostate cancer cell lines is a limitation in the pipeline of preclinical investigations, where patient tumour types are many and varied. Moreover, new models are required to reflect the emerging mechanisms of resistance as new treatments are introduced into practice. There are global efforts to address these challenges, and as Australian endocrinologists with an interest in prostate cancer, we have featured prominently in international collaborations and consortia (Navone et al. 2018). Why is this so?

As scientists and researchers, we embarked on a journey towards developing more relevant prostate cancer models that arose from our training in reproductive endocrinology. Viewing the prostate organ as a complex composition of epithelia and surrounding stromal cells, we acknowledged that cell–cell interactions are necessary for normal hormone action. Initially, we created tissue recombinants of developmental stroma or mesenchyme with epithelia from different sources. Prostatic stroma from a fetus or neonate directed the epithelial differentiation and secretions, which was not possible with adult stroma (Cunha et al. 2002). We employed this remarkable instructive property of developmental mesenchyme to direct the differentiation of human embryonic stem cells into mature prostate epithelia (Taylor et al. 2006). We subsequently learnt that stroma could not only direct but also redirect the differentiation of committed epithelia. Hence, we examined the consequences of recombining stroma from one organ with epithelia from another organ e.g. epithelia from mammary gland and stroma from prostate (Taylor et al. 2009). While the prostatic mesenchyme was endoderm-derived, the mammary epithelia were derived from the ectodermal lineage, and mature epithelium that had previously expressed mammary gland proteins now expressed only prostatic secretory proteins, including PSA a prostate-secretory protein (Taylor et al. 2009). Collectively, these studies highlighted the potential of developmental mesenchyme to provide growth stimulatory signals and induce differentiation to direct epithelial behaviour fate.

**Table 1**  Summary of the treatments for prostate cancer included in the World Health Organisation Model List of Essential Medicines.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formulation</th>
<th>Usage</th>
<th>Therapeutic alternatives</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolin</td>
<td>7.5 mg; 22.5 mg in pre-filled syringe 50 mg tablet 20 mg/mL; 40 mg/mL injection</td>
<td>Metastatic prostate cancer Metastatic prostate cancer Metastatic prostate cancer</td>
<td>Goserelin and triptorelin Flutamide and nilutamide None</td>
<td>GnRH analogue AR antagonist Taxane-based chemotherapy CYP17 inhibitor</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>250 mg; 500 mg tablet</td>
<td>Metastatic castration-resistant prostate cancer Metastatic castration-resistant prostate cancer</td>
<td>Enzalutamide Prednisone</td>
<td>Corticosteroid</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>5 mg; 25 mg tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
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Throughout these studies, it was evident that the survival of recombinant tissue was not possible in vitro and was only achieved in vivo, when engrafted under the kidney capsule of immune-deficient mice. The same technique also enabled successful xenografting of human prostate cancer tissues (Wang et al. 2005, Lawrence et al. 2013, Wang et al. 2016). Using this knowledge and expertise, we recently established the Melbourne Urological Research Alliance (MURAL) collection of prostate cancer PDXs (Risbridger et al. 2021). We have made significant modifications to the protocols we initially employed for tissue recombination. We now reliably engraft almost all patient tumours and 20% of them will become serially transplantable PDXs. These models are becoming critical to preclinical discovery and testing programs in Australia and overseas (Lawrence et al. 2018, 2021, Watt et al. 2019, Nyquist et al. 2020, Porter et al. 2021).

Towards development of more precise models of prostate cancer

We and others employed several basic principles of endocrinology to successfully graft human prostate cancer tissues into mice, which is notoriously difficult to do (Lawrence et al. 2015). These factors included the microenvironment (sub-renal grafting), stromal stimuli, and hormone environment, extended time to establishment (average time to first graft for MURAL PDXs is ~220 days) (Risbridger et al. 2021). Once established as serial transplantable grafts, PDXs can be transplanted to the sub-cutaneous site for ease of monitoring changes in graft volume (Lawrence et al. 2013). Like the MURAL cohort, other groups have established prostate cancer PDXs using sub-renal capsule grafting, such as the Living Tumor Laboratory cohort (LTL; http://www.livingtumorlab.com/) (Lin et al. 2014), while others have used s.c. or orthotopic grafting (Nguyen et al. 2017, Palanisamy et al. 2020). To reveal the extent of the variation of existing PDXs of prostate cancer, several laboratories formed the Movember GAP1 PDX consortium (Navone et al. 2018) (Fig. 2). Cumulatively, this is a large collection of 98 serially transplantable prostate cancer PDXs includes tumours from patients with primary or metastatic disease, who are either treatment naive, have received treatment but are still androgen responsive or who have developed CRPC. In addition, the pathology of these tumours includes prostate adenocarcinoma, neuroendocrine differentiation and mixed phenotypes (Navone et al. 2018).

The MURAL PDX collection consists of 31 primary and 28 metastatic tumours obtained from biopsy, surgery or rapid autopsy samples. The clinical data of patients and the pathology of each PDX have been reported, and of the 59 PDXs, 55% are adenocarcinomas, 31% are neuroendocrine tumours and 14% have mixed pathology. Biomarkers, including the androgen receptor, including the AR, alpha-methylacyl-CoA racemase (AMACR), PSA,
ETS transcription factor ERG (ERG) and neuroendocrine markers, and RNA sequencing and targeted DNA sequencing have been used to classify PDXs. Several PDXs have at least partial loss or mutation of either TP53, RB1, or PTEN and 12 PDXs have alterations of at least 2 of these tumour suppressor genes (Risbridger et al. 2021). Alterations in AR, Wnt, DNA damage repair and PI3K pathways are also represented by these PDXs. A more detailed analysis of the sub-pathologies and growth patterns in each of these PDXs is underway but includes PDXs with ductal adenocarcinoma and adenocarcinoma with focal neuroendocrine differentiation. This detailed focus on pathology is an important feature of the MURAL PDX collection that will enable us to explore the biology of these pathologies in terms of risk stratification and optimal therapeutic strategies.

Armed with an increase in the number of prostate cancer PDXs from several collections, the field is poised to be more sophisticated in designing preclinical studies, tailoring the selection of models to the question more precisely i.e. using a precision medicine approach to the use of PDXs. Despite these advances, there are still technical limitations to using PDXs in discovery research. For example, it is more challenging to perform mechanistic studies involving knockdown or over-expression of candidate genes using PDXs compared to cell lines. In vivo genetic screens have been performed successfully with PDXs from other tumour types, including melanoma (Bossi et al. 2016). With further optimisation, CRISPR or shRNA libraries could also be used with prostate cancer PDXs in future studies.

**Using models to deliver precision in our evaluations of therapeutic efficacy**

Is it possible to exploit the differences among models to more realistically mimic patient diversity? To some extent it is, and we discuss three examples of how models are selected and used to answer specific questions.

**Advancing management of castrate-resistant prostate cancer**

Many therapies initially enter the clinic towards the end of the clinical trajectory for prostate cancer. Even though the number of clinical trials has increased, there is a finite number of patients who have advanced incurable CRPC who can be recruited into trials, and this is a limitation. Appropriate preclinical models could provide another option for testing the timing, sequencing and dosing of therapies before trials are conducted in patients. But this option needs reliable models that generate information that can be translated to the clinic.

Modelling CRPC is more complex than can be captured with AR-responsive or AR-null cell lines (e.g. VCaP, LNCaP, 22Rv1, PC3 or DU145 cells). The mechanisms of resistance to ARSiS include amplifications, mutations and structural rearrangements of the AR and expression of truncated AR variants (Shiota et al. 2022), and these adaptations can be mirrored in PDXs. Using PDXs that encompassed diverse AR resistance mechanisms (PDX-201.1A, PDX-201.2A, PDX-27.1A and PDX-27.2A), it was possible to show sensitivity to the combination of ribosome-targeting agents CX-5461 and CX-6258 (Lawrence et al. 2018). Further studies are underway to examine other combination treatments that are effective across PDXs with diverse phenotypes (Lawrence et al. 2021).

**Tailoring treatments for neuroendocrine prostate cancer**

NEPC is a lethal form of prostate cancer (Wang et al. 2021). While 1–2% of clinical cases arise de novo, an escalating incidence of treatment-induced NEPC has been observed in patients with CRPC via neuroendocrine (NE) transdifferentiation, which has been recognised as a therapeutic resistance mechanism (Beltran et al. 2019). The rarity of de novo NE tumours of the prostate gland, means that there are very few models of this type, often known as pure de novo NE tumours. More commonly adenocarcinomas with NE differentiation are reported at diagnosis. There is no doubt that the pure NE tumours are lethal and patient survival is poor, but the implications and significance of the mixed tumour type (i.e. adenocarcinoma with NE differentiation) are controversial. The evidence on whether or not patients’ tumours of mixed pathologies leads to poor outcome or survival is equivocal, mostly due to variability in detection and reporting as well as follow-up and survival data (Kannan et al. 2022). Nevertheless, there are several useful and informative models that have emerged to improve our understanding of tumours with mixed AR/NE pathology. The MURAL PDX collection includes > 8 models with mixed AR-positive and NE pathologies, one model that is double negative (PDX-201.2A; AR−/NE−) and one which is amphicrine (PDX-387A; AR+/NE+). Significant insights into these rarer tumour types will be gained by investigators pooling resources and combining these models from...
various collections (i.e. MURAL, MDA, LTL, LuCAP) in consortium studies, as it overcomes the limited number of models in individual collections and provides a more comprehensive overview of responses.

A notable gap in our models of CRPC is those that mimic the transition of adenocarcinomas to neuroendocrine tumours that function independently of hormones. This phenotypic change is devastating for patients, as NEPC is unable to be treated. Thus, it remains an intense area of research focus for many investigators. There are several emerging areas of promising therapies, such as epigenetic targets, based on the observation of the changes in epigenetic regulatory mechanisms that are key to the transformation to NEPC (Thompson et al. 2022). However, we are hampered by a lack of models to use to study how to reverse or prevent the emergence of NEPC. While several models of treatment-induced NEPC are included in PDX collections, rarely are there matching PDXs from the primary specimen to study before and after the differentiation to NEPC (Shi et al. 2022). Nevertheless, the Living Tumor Laboratory has established a PDX that develops NE features in vivo under treatment selection. LTL331R is a castration-resistant subtype of LTL331, originally derived from a hormonal-naïve prostate adenocarcinoma, that exhibits NE features characterised by small cell morphology, expression of NE signature genes (e.g. CD56, CHGA, NSE and SYP) and absence of AR as well as its downstream signalling (Lin et al. 2014). Importantly, NEPC was also observed in the donor patient, confirming that the LTL331/331R model could accurately mimic the development and progression of clinical NEPC. Models such as this are rare in PDX collections but will be necessary for determining whether the mechanisms of NE transdifferentiation can be overcome or reversed. To test and demonstrate this convincingly, we need models at different time points in the pathway to NEPC to test efficacy during and after transition from adenocarcinoma to NEPC, and this remains a future challenge for the field.

**Improving treatments for castrate-sensitive prostate cancer**

The development of models of castrate-sensitive prostate cancer might seem much simpler, but it has proven to be just as complex. A common source of tumour tissue is from men who undergo radical prostatectomy. This surgery is performed with curative intent, usually for men whose tumours are deemed to have a moderate to high risk of progressing. While there is usually plenty of tissue to engraft, the take rate and the development of serially transplantable PDXs are lower than for CRPC models (Risbridger et al. 2021). Nevertheless, PDXs from castrate-sensitive prostate cancer have provided valuable insights into the significance of sub-pathologies that exist in primary tumours, such as IDC-P and ductal adenocarcinoma (Lawrence et al. 2020). The prevalence of IDC-P is as high as 36.7% in high-risk prostate cancer and 56.0% in metastatic or recurrent disease and is present in tumours following androgen deprivation therapy or chemotherapy (Porter et al. 2017). Ductal prostate adenocarcinoma is another aggressive histological variant of prostate cancer. A recent study demonstrated that patients with ductal adenocarcinoma who underwent surgery or radiotherapy had worse outcomes than patients with acinar adenocarcinoma patients and that upregulation of several intrinsic resistance pathways in ductal adenocarcinoma rendered ADT less-effective (Ranasinghe et al. 2021). Together, IDC-P and ductal adenocarcinoma are emerging pathologies that predict poor patient outcome, and studies in PDXs have alerted the need for clinicians to report them to improve subsequent decision-making and will aid the developments of more effective therapies for patients.

**Conclusions**

Rapid advances in the clinical management of patients with prostate cancer across the stages of disease progression are evolving to provide precision medicine approaches. These developments include the identification of high-risk features at diagnosis, introduction of upfront intensive combination therapies for patients with advanced disease and several new treatment options for CRPC, which remains lethal. Herein, we have discussed how the scientific understanding of hormone action and development of the prostate gland have led to these impactful discoveries. The use of hormone therapies to treat prostate cancer has changed significantly over time, and the emergence of ARSIs has improved outcomes for patients with CRPC. However, the emergence of treatment-induced NEPC remains a challenge for the field. The development of clinically relevant patient-derived prostate cancer models, which were established based on a fundamental understanding of endocrinology, and the role of stroma and hormones in normal and developmental tissues, will allow further refinement of our knowledge of prostate cancer aetiology and underpin future research discoveries that will be translated to clinical practice.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Data availability
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