Prostate epithelial cell differentiation and its relevance to the understanding of prostate cancer therapies

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ABSTRACT
Prostate cancer is the most common malignancy in males in the western world. However, little is known about its origin and development. This review highlights the biology of the normal prostate gland and the differentiation of basal epithelial cells to a secretory phenotype. Alterations in this differentiation process leading to cancer and androgen-independent disease are discussed, as well as a full characterization of prostate epithelial cells. A full understanding of the origin and characteristics of prostate cancer epithelial cells will be important if we are to develop therapeutic strategies to combat the heterogeneous nature of this disease.

INTRODUCTION
The incidence of prostate cancer has increased over the past decade and it is now the most common non-cutaneous malignancy in Europe and North America [1]. Radical prostatectomy and radiation therapy are the current treatments for curative intent for patients with early disease, with androgen ablation therapy being the mainstay for progressive prostate cancer [2]. Androgen ablation therapy leads to apoptosis of the androgen-dependent tumour cells with an associated decrease in PSA (prostate specific antigen) levels. However, most men will eventually fail this therapy and die from recurrent AIPC (androgen-independent prostate cancer). At present, there is no effective therapy for AIPC.

Despite significant research, we still have a limited understanding of the biology of the prostate. To understand the aetiology of prostate cancer it is crucial to understand the normal growth and development of the prostate. Over 90 % of prostate tumours are adenocarcinomas that arise from the glandular epithelium of the prostate. Since prostate cancer is epithelial in nature, understanding the differentiation process of prostate basal cells to secretory luminal cells will help us to define the phenotype of prostate epithelial tumour progenitor cells.

CHARACTERIZATION OF PROSTATE EPITHELIAL CELLS
The prostate consists of glandular epithelium embedded in a fibro-muscular stroma (Figure 1a). The epithelium is composed of two histologically distinct layers (Figure 1b). The secretory luminal layer is made up of tall columnar cells that are responsible for the production of PSA, PAP (prostatic acid phosphatase) and human kallikrein-2 that are secreted as part of the seminal fluid [3,4]. This layer of cells is underpinned by a basal layer of cuboidal epithelial cells. This in turn is lined by a basement membrane consisting of extracellular matrix which forms a divide between the basal cells and the stroma [5].

Key words: androgen, cancer therapy, epithelial cell differentiation, growth factor, prostate cancer, stem cell.
Abbreviations: AIPC, androgen-independent prostate cancer; CK, cytokeratin; DHT, 5α dihydrotestosterone; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; KGF, keratinocyte growth factor; NE, neuroendocrine; PAP, prostatic acid phosphatase; PSA, prostate specific antigen; PSCA, prostate stem cell antigen; PSMA, prostate surface membrane antigen; TGF, tumour growth factor.
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Isaacs and Coffey [6] hypothesized that the basal layer also contains a stem-like cell population that is responsible for the development of all epithelial cell types in the prostate. They proposed that when the stem-like cell undergoes mitosis it gives rise to two cells, another stem cell and a daughter progenitor (transit amplifying) cell which, in turn, differentiates into a terminal end-stage secretory luminal cell.

Three main epithelial cell types have been identified in prostate epithelium, as mentioned previously, the basal and luminal cells, and also an NE (neuroendocrine) cell population. Traditionally basal and luminal cells were considered to be two distinct cell types; however, we now know that the differentiating transit amplifying cells give rise to heterogeneous subpopulations of cells as they migrate from the basal layer into the luminal layer (Figure 1c) [7–9]. The heterogeneous population of cells that express an intermediate phenotype between that of the early progenitor basal cells and the terminally differentiated secretory cells are termed ‘intermediate cells’ [7,8]. Most work has concentrated on the characterization of the basal and luminal layers as opposed to individual cell types and, as a result, there is limited data about the changing epithelial cell phenotypes during differentiation.

**NE cells**
The NE cells are sparsely scattered between the basal and luminal layers [10]. They are also thought to arise from the stem cells in the basal layer [11–13], although there is some evidence to suggest that they may be neuronal in origin [14]. The NE cells are androgen-independent [15] and are considered to be non-proliferating terminally differentiated cells that express neither the androgen receptor [16] nor the anti-apoptotic oncogene Bcl-2 [13]. The exact role and function of these cells is not completely understood, but it is believed that they may play a role in the growth and differentiation of the developing prostate and have been implicated in carcinogenesis [17,18]. NE cells are characterized most commonly by the expression of chromogranin A [19], and other markers, such as serotonin [20,21], bombasin [22], VIP (vasoactive intestinal peptide) [23,24], calcitonin [25–27] and parathyroid hormone-related proteins, also indicate an NE origin [28,29].

**Basal cells**
The basal layer is believed to be the proliferative compartment of the prostate [30,31]. It consists of androgen-independent cells that express high-molecular-mass CKs (cytokeratins), with CK5 and 14 and the cell-surface marker CD44 being the most common markers used to characterize them [8,32–35] (Figure 1c). Other markers include CK10, 11, 15 and 17 [9,36,37], p63 [38] (a homologue of p53), the integrin α2 [39], the anti-apoptotic protein Bcl-2 [40–43], P-cadherin, [44,45], the nuclear phosphoprotein pp32, [46] GST-π (glutathione S-transferase-π) [47,48], c-MET [the membrane receptor for
HGF (hepatocyte growth factor) [49,50] and HER-2 [human EGF (epidermal growth factor) receptor-2] [51].

**Luminal cells**

The luminal layer consists of androgen-dependent cells that require androgens for survival and upon androgen withdrawal undergo apoptosis and die. They express low-molecular-mass CKs and are characterized most commonly by CK8 and 18 and the cell-surface marker CD57 [32,35,52,53] (Figure 1c). The androgen receptor is also present [6,54], mediating the production and secretion of PSA and PAP [55]. ET-1 (endothelin-1) is present in normal luminal cells, and low levels of PSMA (prostate surface membrane antigen) have also been detected [56–58]. As a result of the differentiation process, luminal cells do not express detectable levels of Bcl-2 [41,42].

Subpopulations of cells in the luminal layer that express only CK8 or 18 have also been identified [59]. Along with the CK8/18-positive cells, these may represent separate groups of terminally differentiated cells (Figure 1d).

**Intermediate cells**

Using histology, luminal and basal cells were defined based on their tissue morphology and cell-type-specific markers were then identified. CK5 and 14 are present in the basal layer, whereas CK8 and 18 are used to denote the luminal layer. However, further studies noted that some cells in the basal layer express luminal markers, whereas basal markers were seen in the luminal layer. These findings suggest that the prostate epithelium consisted of heterogeneous populations of cells. Many cells express similar markers, with specific cell phenotypes being identified using combinations of markers, such as the CKs, cell-surface markers, anti-apoptotic proteins and cell cycle regulators. The cells that express combinations of markers common to both the basal and luminal epithelial layers are termed ‘intermediate cells’ (Figure 1c).

*In vivo* immunohistochemical analysis of prostate tissue identified two intermediate phenotypes based on their CK expression, a CK5/14/18 population of cells [8] and a CK5/18-positive population [7,8,60]. Interestingly, CK5/18 cells were identified in both basal and luminal layers. These cells may represent an intermediate cell type that migrate from the basal to the luminal layer. This suggests that, as cells differentiate towards a luminal phenotype, they lose CK14 expression prior to their loss of CK5. Other CK markers include CK7, 17 and 19, with CK19 the only CK specific for intermediate cells [9,59,61].

*In vitro*, a total of five different intermediate types have been identified (Figure 1c). These include CK5/14/18 [8,62], CK5/18 [8], CK14/8 [59,63], CK14/18 [37] and CK5/14/8 [64,65]. However, the latter three subsets have not been identified *in vivo*, which may demonstrate an *in vitro* artefact or their low abundance *in vivo*.

*In vitro* studies have also yielded other potential markers. PSCA (prostate stem cell antigen) can be used to subdivide basal CD44-positive cells into two distinct populations [62]. The CD44-positive/PSCA-negative population have been shown to be early undifferentiated cells, whereas the CD44-positive cells/PSCA-positive cells are a differentiated population (Figure 1c). The basal marker p63 can also be used to subdivide the same populations, with the early cells being positive for p63, with later CD44-positive cells being negative for p63.

Markers that have been considered specific for the luminal layer, such as PSA and the androgen receptor, have been occasionally identified in the basal layer [66–69]. This raises the question as to whether cells are continually differentiating in the prostate or whether they remain at particular points (e.g. early basal cell or an intermediate cell) until they are required to become terminally differentiated into a secretory luminal cell. If the latter were true, then some cell phenotypes may only be identified at precise time points during differentiation and growth of the prostate. This may explain why only certain phenotypes are occasionally found in the basal layer, for example basal cells expressing the androgen receptor may only be transiently in the basal layer prior to migrating into the luminal layer. However, in culture, it may be possible to study these cells more extensively. For example, Fry et al. [59] noted that only 1:1000 cells co-expressed CK14 and 18 *in vivo*, whereas these cell types are commonly found in culture [59,62]. One possible explanation for this is that these cells are not exposed to the appropriate feedback mechanisms that exist *in vivo* and can be cultured with prolonged transient time points in the differentiation process.

The terms basal and luminal cells are adequate when referring to cells that are specific for each layer. However, differentiating cells that are migrating between both layers are not as easily classified, as one particular phenotype may be located in either layer. Classifying cells according to specific differentiating phenotypes may allow us to clearly define this group of intermediate cells. For example, expression of the androgen receptor is a definitive point in the differentiating process, as cells that do not express it are less differentiated and all cells that express are progressing to a terminally differentiated phenotype. The classification of cells according to their expression profiles, as opposed to their anatomical location, may prove more reflective of their true phenotype.

**PROSTATE EPITHELIAL STEM CELLS**

The main evidence to support the presence of stem cells in the prostate has come from studies of the rat prostate. Following castration, the luminal cells (which consist of over 90% of the prostate epithelium) undergo apoptosis leaving the basal layer intact [70,71]. Re-administration of androgens renews the prostate epithelium to its original
fully functional state. Subsequent androgen withdrawal and re-administration confirms further the capacity of the prostate epithelium for self-renewal [46,72]. The fact that the basal layer remains intact following castration and re-administration of androgens results in the regeneration of a secretory layer suggests the presence of an amplifying cell population residing in the basal layer.

Attempts to identify and isolate prostate stem-like cells have proven difficult. The most widely accepted stem-like cell model is that of an early basal cell phenotype residing among the CK5/14-positive cells that give rise to cells that progressively differentiate into terminally differentiated cells [73]. Another proposed model is where a stem cell may express all the markers of the intermediate phenotype and lose either the basal or luminal markers when it differentiates into a luminal or basal cell respectively [64].

In recent years, both colony formation and cell-surface adhesion markers have been used to identify this group of cells. Collins et al. [39] have demonstrated that integrins may be used to identify stem-like cells in the prostate. Basal cells from primary cultures were sorted using the basal cell-surface marker CD44. Having identified α2-integrin on the cell surface of one cell population, they [39] demonstrated that only the cells expressing the α2-integrin differentiate into cells with associated secretory activity similar to that found in vivo.

Hudson et al. [63] have identified colonies that display three different phenotypes of basal, intermediate and luminal cells. They also looked at the integrin expression of each colony type but found no correlation. Collins et al. [39] also looked at colony formation and again identified three colony types of different sizes; however, they were also unable to correlate integrin expression with different colony types. This may indicate that prostate stem cells do not form small subunit colonies but are scattered among the subpopulations of basal cells as found in other tissues [74].

p63 represents another potential stem cell marker. It has been identified as an early basal cell marker, but is more likely to represent a population that contains stem cells rather than being specific for them [38,62,75].

THE ROLE OF EPITHELIAL–STROMAL INTERACTIONS IN THE DIFFERENTIATION PROCESS

The extracellular matrix, stromal growth factors and androgens are essential for functional and morphological differentiation of prostatic epithelium [35,76–82]. The process of differentiation, however, involves complex interactions between the stromal matrix and epithelium which maintains a balance between proliferation, differentiation and apoptosis. The rates of apoptosis and proliferation differ significantly between the basal and luminal compartments, resulting in a regional heterogeneity of cell turnover [83–85].

The main androgen metabolite in the prostate is DHT (5α dihydrotestosterone) and is essential in the stimulation and production of stromal growth factors. DHT binds to stromal androgen receptors and mediates the release of growth factors which, in turn, act directly on epithelial cells to drive differentiation [76,86,87]. The binding of DHT to epithelial androgen receptors results in the production of prostastic secretions such as PSA and PAP. The direct role of DHT in differentiation of prostate epithelium has, however, not yet been elucidated [86,88].

Extracellular matrix is essential for three-dimensional culture growth. In vitro models that contain an extracelluar component have proven successful in differentiating human prostate epithelial cells from early precursor cells into fully functional terminally differentiated cells [76,80,81]. The same models have also demonstrated that the presence of both stroma and DHT are essential. The prostate extracellular matrix consists of type IV collagen [89], laminin [90] and heparin sulphate proteoglycan [91]. The exact role of each of these components in differentiation of the prostate epithelium is poorly understood; however, the main function of the extracellular matrix is to form polarized cellular domains via cytoskeletal re-arrangement induced by cell adhesion to extracellular matrix, which is mediated by integrins [92,93], and also by epithelial cell–cell adhesion [94]. The spatial arrangement and establishment of cell polarity is fundamental to the cellular process of differentiation, which is influenced further by growth factors.

Prostate stroma is capable of producing at least eight families of growth factors [95], some of which are essential for differentiation, whereas others are involved in proliferation and growth inhibition. Of these, five families are known to be involved in the regulation of proliferation and differentiation of the epithelium, these include TGF (tumour growth factor), FGF (fibroblast growth factor), IGF (insulin-like growth factor), EGF and HGF families.

IGFs are functional homologues with insulin that have marked mitogenic effects on prostate epithelial cells [96,97]. IGF has two isoforms, IGF-I and IGF-II, with IGF-I being the more potent mitogen [98]. The type I IGF receptor has an affinity for both IGF-I and IGF-II and is present in basal cells [99]. The presence of IGF in culture of primary epithelial cells is essential and, in studies looking at the effects of different factors on the growth and proliferation of the epithelium, IGF has been shown to be the most powerful mitogen [88,100,101].

The FGF family consists of 10 members of which seven have been identified in the prostate (FGF-1, -2, -3, -5, -7, -8 and -10) [102–106]. All members can signal through common receptors and are mitogenic to the stroma, apart from KGF (keratinocyte growth factor or FGF-7) and FGF-10, which stimulates proliferation of epithelial cells.
directly [106–108]. The expression of FGFs and their receptors is not fully understood; however, receptors have been identified in both the stroma and epithelium. Basic FGF has been shown to stimulate proliferation of stromal but not epithelial cells [87,109,110], whereas acidic FGF (FGF-1) is not present in the normal prostate, but is present in BPH (benign prostatic hyperplasia) and dysplastic luminal cells [111].

TGF-β1 is the predominant isoform in the TGF-β family and plays an important role in the regulation of prostatic differentiation and prostate cancer cell growth [112–114]. In benign prostatic epithelium, its action is mediated through a paracrine mechanism, where it inhibits proliferation and induces apoptosis in the prostate epithelium [115]. TGF-β1 also has an inhibitory influence on proliferation of stromal cells that may be partially overcome by FGF-2. This indicates the importance of TGF-β1 in prostate epithelial cell turnover and in maintaining prostate epithelial homeostasis [110,116].

EGF stimulates the growth of the epithelium [88,101,117,118]. TGF-α, a member of the EGF family, binds to the same receptor as EGF and is considered to have a role in the differentiation of the prostate epithelium [119].

HGF/scatter factor receptor c-MET is located in the basal layer of the prostate epithelium and can inhibit proliferation and cause differentiation in normal prostate epithelial cells [49,50].

Although the growth factors mentioned above play a role in the homeostasis of the prostate, other factors have also been implicated in the differentiation process. For example, retinoic acid inhibits cell proliferation and promotes differentiation in vitro and in vivo [120,121] and has also been shown to influence the cytoarchitecture of prostate cancer cells [122]. Alterations in the stromal environment have also been implicated in prostate carcinogenesis, as tumour stroma has been shown to differ from normal stroma [123–126]. If alterations to the environment have such dramatic effects on the prostate epithelium, what is the consequence of deleting any one of the essential components of the differentiation environment (stroma, growth factors or androgens)? It is likely that remaining differentiation factors will still drive cells to differentiate but ‘inappropriately’ if a required differentiation component is absent.

**ORIGIN OF PROSTATE CANCER**

To understand the initial phase of carcinogenesis it is imperative that the cell of origin of prostate cancer is identified. Classically this was thought to originate from luminal cells of the prostate epithelium, as tumour cells express luminal characteristics such as secretion of PSA and the expression of CK8 and 18 [32,53,127]. However, it has been demonstrated clearly that most AIPCs express basal cell characteristics, such as the expression of Bcl-2, contributing to their apoptotic-resistant phenotype [41].

It has been considered that prostate cancer cells may either acquire basal characteristics or may fail to lose some of their basal characteristics during tumour growth and development.

As prostate tumours express both basal and luminal characteristics, studying the different intermediate cell populations may lead to a better understanding of cancer phenotypes. For example, PSCA is overexpressed in prostate cancer [128], whereas p63 is rarely expressed [75]. Tran et al. [62] examined p63 expression in normal intermediate CD44/PSCA-positive prostate epithelial cells and demonstrated that, in normal PSCA-expressing cells, p63 is absent. This suggests that normal intermediate cells express similar markers to that of tumour cells and supports the theory that the origin of prostate cancer is an intermediate cell.

van Leenders et al. [129] and van Leenders and Schalken [130] have shown that proliferative inflammatory atrophy, which is considered a possible precursor lesion for prostate cancer, consists predominantly of an intermediate cell phenotype by demonstrating co-expression of CK5 and 18. Similar findings were also described by Parsons et al [75], van Leenders et al. [131] also characterized androgen-dependent and -independent primary tumours and metastatic cell lines and found that all prostate cancer cells expressed the luminal marker CK18. The basal marker CK5 also was present in both the androgen-dependent and -independent cells, with increased levels in the androgen-independent cancer cells. This would correlate with the normal prostate cell populations, as CK5 would be present in earlier androgen-independent cells and would decrease as the cancer cells differentiated into an androgen-dependent phenotype.

The nuclear phosphoprotein pp32, which is expressed in prostate basal cells, is expressed in nearly all prostate tumours and is highly expressed in high-grade tumours [132]. This protein, together with PSCA, p63 and CK5, may prove useful in identifying subpopulations in prostate tumours and their role in tumour progression and metastasis.

**PROSTATE CANCER DIFFERENTIATION**

Many tumours are considered to originate from a single cell that differentiates to give heterogeneous cell types. The evidence for this has come from the identification of cancer stem cells in leukaemias [133] and, more recently, in breast and brain tumours [134–136]. The possibility of a single cell of origin for prostate cancer that behaves as a stem-like cell and gives rise to a heterogeneous tumour type may have many implications for treatment of prostate cancer and understanding AIPC.

To date, prostate cancer stem cells have not been identified. However, support for prostate tumour cell differentiation from less differentiated cells has been shown. Lang et al. [81] studied the metastatic PC3
prostate cell line that does not express the androgen receptor or produce PSA. When the cells were cultured in three-dimensional culture systems, they demonstrated that tumour cells could be differentiated into glandular type spheroids that produce PSA.

Further support for prostate tumour differentiation has been demonstrated with the LNCaP epithelial tumour cell line. These cells can be differentiated into an NE phenotype following treatment with IL-6 (interleukin-6), dibutyrate cAMP or in steroid-depleted medium [137–139]. NE differentiation has also been shown to arise from androgen-independent human primary tumour cells when grown in a nude mouse model following castration [140].

From our understanding of the differentiation process, we hypothesize that normal cells differentiate appropriately in their optimum environment. However, due to a change in this cellular environment, inappropriate differentiation may occur leading to the initiation of a cancer phenotype. Applied specifically to the prostate, we believe that this occurs during the process of differentiation from an androgen-independent to androgen-dependent phenotype (Figure 2a).

**ORIGIN OF AIPC**

Numerous theories have been proposed for the mechanisms of progression of prostate cancer to an androgen-independent state. Initially, prostate tumours appear to consist of an androgen-dependent phenotype and, upon withdrawal of androgens, tumours regress and circulating PSA levels are reduced to negligible biochemical levels. However, a proportion of the tumour cells survive and progress in an androgen-independent fashion.

Androgen-independent disease may arise from androgen-dependent cells that gradually assume the anti-apoptotic properties of basal cells. This may be due to various genetic alterations that may occur during disease progression or androgen-ablation therapy [141]. A lot of interest has also concentrated on the androgen receptor in the progression of AIPC [142].

If progression was simply due to activation of the androgen receptor by other mechanisms, we should expect the tumour cells to have the characteristics of the androgen-dependent prostate epithelial cell. We know that AIPC consists of less differentiated more aggressive tumours that are phenotypically dissimilar to their androgen-dependent counterparts. Why then do some androgen-independent tumours produce PSA? This may be due to inappropriate differentiation. Alterations in the androgen receptor may play a role in androgen-independent disease, but may only be involved in the proliferation and progression of androgen-independent cells.

Previously, Isaacs and Coffey [143] demonstrated in the Dunning prostate cancer rat hind flank model the possibility that androgen-independent cells are originally present in androgen-dependent tumours and, following androgen ablation, these cells survive and proliferate [143]. This androgen-independent growth is associated with increasing levels of Bcl-2, contributing to the survival of tumours [144]. This concept has become more popular in recent years and is also supported by the fact that cells with a phenotype similar to normal basal cells are more pronounced in AIPC [8].

We propose that prostate cancer arises from the basal layer and that androgen-dependent tumours consist of heterogeneous cell types that may include androgen-independent cells. Evidence for this is supported by Liu et al. [145], who used the cell-surface markers CD44 and CD57 to calculate the ratio of basal to luminal cells in primary prostate tumours. They showed that tumours do contain a heterogeneous ratio of basal to luminal cells that varies depending on the aggressiveness of the tumours, with more advanced tumours expressing a more basal phenotype.

Why androgen-independent cells proliferate after androgen ablation therapy is not understood. Above, we proposed that the principles of normal differentiation may also have relevance in cancer. To try and understand AIPC we propose further that the principles of differentiation and proliferation may have direct relevance to its progression. One of the fundamentals of the differentiation process is that cells tend to decrease or cease proliferation [146]. Thus androgen-independent tumour
cells in an androgen environment may not normally proliferate but differentiate to a slow-growing androgen-dependent phenotype. So, in an androgen environment, androgen-independent cells may only represent a small proportion of the tumour. However, in an androgen-depleted environment, androgen-dependent tumour cells will undergo apoptosis. The lack of androgen may prohibit androgen-independent cells from differentiating and allow them to proliferate more rapidly, thus leading to the progression of AIPC (Figure 2b). Studies by Craft et al. [147] support this hypothesis, as they demonstrated in an androgen-dependent mouse tumour model that, after castration, outgrowth of androgen-independent cells occurred from a small subpopulation within the remaining tumour.

CLINICAL IMPLICATIONS

Androgens are required for the proliferation and maintenance of the luminal secretory layer of the prostate epithelium and withdrawal causes these cells to undergo apoptosis. Based on this concept, castration therapies such as androgen ablation have been adopted for the treatment of prostate cancer. However, even after initial biochemical responses, patients will inevitably develop androgen-independent disease. The fact that the basal layer remains following castration would indicate that the prostate gland has the potential to develop tumours depending on the differentiation signals these basal cells receive.

Intermittent androgen-ablation therapy may provide a solution to the selection of an androgen-independent tumour phenotype. On initialization of ablation therapy, there will be an initial biochemical remission as androgen-dependent cells undergo apoptosis. The androgen-independent cells that survive may then begin to proliferate. Cessation of ablation therapy will lead to androgens rising back to normal levels, which will then allow differentiation of the androgen-independent cells into the less aggressive androgen-dependent cells, reducing the proliferation of independent cells. Re-introduction of ablation therapy will cause apoptosis of the dependent cells. Continuation of intermittent therapy may halt the proliferation of androgen-independent cells by intermittently allowing them to differentiate. If there is a role for intermittent therapy, the timing of cessation and re-introduction of therapy will be crucial as, once androgen-independent cells undergo changes independent of the normal differentiation pathway, the ultimate cascade of events leading to hormone AIPC may be initiated. Intermittent therapy may of course not ultimately influence a patient’s final prognosis and may only lead to longer periods of biochemical-marker-free disease. Whether this strategy will improve patient survival remains to be seen.

Ultimately successful therapy for prostate cancer will involve targeting all tumour cells and not just one particular phenotype. Characterization and understanding of the apoptotic phenotype of normal prostate cells will help us to identify and target pathways that induce apoptosis in early tumours. Further phenotyping of more advanced disease will help in understanding the alterations in the apoptotic pathways that allow tumours to become more resistant to therapies. However, in advanced disease, the cells are poorly differentiated and have a greater number of chromosomal abnormalities, mutations and altered methylation states that may give rise to tumour phenotypes. Treatment of metastatic cancer will always provide therapeutic dilemmas as one therapy that is effective for one tumour type may have no beneficial effects on other tumour types. Depending on the differentiation status of tumour cells, different phenotypes may respond differently to different therapies. Understanding particular therapies, their precise mechanisms of action and which cell types they are specific for will help treatment strategies to be refined in targeting specific cancer cells.

CONCLUSIONS

Currently there are no effective treatments for locally progressive and metastatic prostate cancer. Understanding the biology of the prostate and prostate tumours may help focus new research and the development of effective therapies. Future treatment strategies for prostate cancer may involve tumour phenotyping following prostate biopsy, so that the correct therapy may be customized to individual tumours. Ultimately, we believe that the key to correctly targeting both early and advanced prostate cancer will lie in understanding the differentiating phenotypes of both normal and tumour cells.

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