New Roles for Nuclear Receptors in Prostate Cancer

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Abstract

Prostate cancer has, for decades, been treated by inhibiting androgen signalling. This is effective in the majority of patients, but inevitably resistance develops and patients progress to life-threatening metastatic disease – hence the quest for new effective therapies for "castrate-resistant" prostate cancer (CRPC). Studies into what pathways can drive tumour recurrence under these conditions has identified several other nuclear receptor signalling pathways as potential drivers or modulators of CRPC.

The nuclear receptors constitute a large (48 members) superfamily of transcription factors sharing a common modular functional structure. Many of them are activated by the binding of small lipophilic molecules, making them potentially druggable. Even those for which no ligand exists or has yet been identified may be tractable to activity modulation by small molecules. Moreover, genomic studies have shown that in models of CRPC other nuclear receptors can potentially drive similar transcriptional responses to the androgen receptor, while analysis of expression and sequencing databases shows disproportionately high mutation and copy number variation rates among the superfamily. Hence the nuclear receptor superfamily is of intense interest in the drive to understand how prostate cancer recurs and how we may best treat such recurrent disease. This reviews aims to provide a snapshot of current knowledge of the roles of different nuclear receptors in prostate cancer, a rapidly-evolving field of research.

Introduction

Prostate cancer is initially an androgen-dependent disease, and inoperable cases are treated using hormone therapy including androgen ablation (downregulation of androgen production and steroid synthesis inhibitors), and antiandrogens that act at the level of the androgen receptor (AR). The AR is a ligand (androgen)-activated transcription factor, a member of the nuclear receptor (NR) transcription factor superfamily. This numbers 48 members in humans, and while not all are associated with ligands, because many NRs bind and are activated by small molecules easily passing through biological membranes and modifiable by drug design, they potentially represent highly "druggable" targets for therapy and so are a rich source of potential drug targets including for clinically approved drugs – in 2006, 13% of all FDA-approved drugs targeted NRs (Overington, et al. 2006). Members of the NR superfamily are involved in the sensing of environmental and metabolic cues such as hormones, dietary factors, sunlight and thence regulation of key pathways regulating cellular survival, proliferation, differentiation, homeostasis and metabolism (Robinson-Rechavi, et al. 2003). The superfamily is commonly broken down, based on either sequence homology or DNA-binding/dimeric partner specificity (Figs 1B, 2A), into 3 or 4 groups that include (i) the steroid receptors, (ii) the obligate heterodimeric partners of retinoid receptors, which includes retinoic acid /thyroid hormone receptors and (iii) so called "orphan" receptors for which no endogenous ligand has been identified (although given that for many receptors previously termed orphans ligands have been found, making them "adopted orphans", that ligands exist cannot be ruled out). Orphan receptors can be subdivided into those that bind DNA as dimers and those that bind as monomers. Although different categorisation systems are not directly comparable, these are broadly accepted categories (Mangelsdorf, et al. 1995; Nuclear Receptors Nomenclature 1999; Robinson-Rechavi et al. 2003). Here, the receptors are discussed within broadly functional groupings.

Nuclear receptors range in size from a little over 400 amino acids (COUPTF, vitamin D receptor) to almost 1000 (the mineralocorticoid receptor, MR) (Fig. 1A). They are encoded by genes usually consisting of 8 exons, and have a modular structure with 4 main functional domains, reflected in the exon/intron organisation of the gene. These are: (i) The N-terminal domain, which contains transcriptional activation function(s) and interacts with cofactors. This is highly variable in length, shows little conservation or structure, and is encoded by a single exon; (ii) The DNA-binding domain (DBD). This is encoded by 2 exons, each of which encodes a single zinc-finger-like motif, and is the most highly conserved region; (iii)

The "hinge" region. This often contains a nuclear localisation signal and in some (notably the thyroid and retinoic) receptors has a role in transcriptional silencing. It is of variable size and poorly conserved; (iv) The ligand-binding domain (LBD); as well as containing the ligand-binding pocket this is involved in dimerization, transcriptional regulation (it contains another activation function) and interactions with heat-shock proteins and cofactors. It is encoded by 5 exons and is relatively well conserved both in sequence and structure – containing 11 or 12 alpha-helices that realign upon ligand binding to form coregulator-binding surfaces (Mangelsdorf et al. 1995; Robinson-Rechavi et al. 2003; Wurtz, et al. 1996). Every NR achieves its transcriptional effects in concert with a number of coregulator proteins. These comprise coactivators, which increase activity of the receptor and in general are recruited to the activated, ligand-bound receptor, and corepressors, which decrease receptor activity and may be recruited in the presence of inhibitory ligands (antagonists)(Bevan and Parker 1999; McKenna and O'Malley 2002). The list of coregulators is ever expanding, with hundreds reported to date (Heemers and Tindall 2007). The methods by which coregulators affect AR action are diverse, and include promoting recruitment of transcriptional machinery, remodelling chromatin, modifying histone proteins and enzymes, or acting as chaperones (Chmelar, et al. 2007; Jia, et al. 2008). Further, their effects on gene transcription appear to be gene specific and cell lineage/differentiation state specific.

While androgen ablation and antiandrogens are very effective initially in prostate cancer treatment, it is almost inevitable that resistance will eventually occur and men progress to advanced, castration-resistant prostate cancer (CRPC). This stage was once termed "androgen independent" but this was felt to be misleading since although the tumours recur in low androgen conditions, the majority remain dependent on the AR signalling pathway for growth. The mechanisms by which the AR axis is activated in these tumours include: amplification or increased expression of the AR leading to increased AR protein and sensitivity to low or weak androgens; mutations in the AR leading to amino acid substitutions that allow promiscuous activation of the receptor by other, non-androgen ligands including oestrogens, antiandrogens and glucocorticoids; constitutively active forms of the AR lacking the ligand-binding domain; altered ratios of coactivator and corepressor proteins that tip the balance in favour of active AR (reviewed in (Sharifi 2013)). Although it remains the case that the vast majority of advanced prostate tumours retain AR expression, often at higher levels than primary tumours, in recent years evidence has been emerging that other members of the NR superfamily can also contribute to prostate tumour growth – either independently or in concert with the AR. This is of enormous interest both in terms of explaining how prostate

cancer progression occurs and resistance to therapy emerges, but also to provide further rational drug targets - and repurposing of existing NR-targeted drugs – to combat this increasingly common form of cancer, which is the second biggest cancer killer in Western men. This review aims to provide a brief summary of current evidence regarding NRs with known and emerging roles in prostate cancer.

Evidence for NR Alterations in Prostate Cancer

To begin this review, we analysed the 48 known nuclear receptors in publically available TCGA data sets via cBioPortal (Cerami, et al. 2012; Gao, et al. 2013)(Full detailed data in Supplementary Table 1). We also grouped the NRs into different groups based on ligand interactions, which is how we discuss them throughout the article. Analysis of copy number variation and mutations revealed that the frequency of NR alterations is very prominent. Changes in copy number are more frequent than mutation (Figure 2 B,C). Only two of the available studies found changes in copy number in less than 10% of patients, whilst mutations were commonly reported in around 5-15% of patients. Interestingly, from these datasets it is apparent that CNA and mutations are more commonly detected in the metastatic sites than the primary sites, this could mean that such changes in NRs drive cancer progression, or are actually selected for during progression. Analysing all the cohorts together revealed that 16% of patients had alterations in AR, making it the most prominent alteration. This was followed by HNF4 alterations (10% of patients), and the orphan receptor, NR2E1, or TLX (8% of patients). When we evaluate via the aforementioned groups (Figure 1D), out of a total of 1387 patients, we get a variation in the percentage of patients with alterations in: steroid receptors (27.9%), other liganded receptors (34%), metabolic receptors (16.9%), and orphan receptors (60.2%). However, the groups are comprised of different numbers of receptors, and when we adjust for these numbers, steroid receptors have the most alterations per receptor, occurring on average in 65 patients per receptor, followed by other liganded (43 patients per receptor), orphan receptors (39 patients per receptor), and metabolic receptors (34 per receptor). These data confirm that alterations in nuclear receptors are highly prominent in prostate cancer and identify that they may have key roles in pathophysiology of prostate cancer.

Steroid Receptors

Androgen Receptor (AR or NR3C4)

Tumours not cured by surgery or radiotherapy are treated by blocking the action of AR. However, despite this it has only been since the mid-90s that we have become aware of the

importance of androgen signalling in prostate progression. This was on the basis of improving technology, which allowed for the detection of AR in relapsed tumours in metastatic sites (Hobisch, et al. 1995; van der Kwast, et al. 1991). This also prompted widespread adoption of the term castrate resistant prostate cancer (CRPC), as opposed to androgen independent disease.

While the majority of NRs are, as implied by the name, localised to the nucleus, the AR is one of the few that cycles from the cytoplasm to nucleus upon activation by its cognate ligand, the most potent of which and the predominant in prostate is dihydrotestosterone (DHT). The role of AR appears to change with cancer progression. In benign and early tumourgenesis, AR is involved in differentiation, but this is switched with malignancy, where AR drives proliferation (Gao, et al. 2001). This is potentially the culmination of a change in the pattern of AR binding; in malignancy AR binds to and enhances transcription of genes involved in proliferation that aren't regulated in benign conditions (Memarzadeh, et al. 2011). In genetically modified mice models AR over-expression is associated with development of PIN, but not full de-differentiation toward cancer (Stanbrough, et al. 2001), and mutated AR levels in mice leads to development of adenocarcinoma in the ventral lobe (Han, et al. 2005). Evidence in humans is limited, although comparison of genome-wide analysis from prostate bud elongation with genes known to be involved in cancer, identified several such AR-regulated genes overlapping with genes known to drive cancer initiation (Pritchard, et al. 2009; Tomlins, et al. 2007). Despite showing a change in AR action toward pro-proliferation, there is limited evidence for a role of epithelial AR for cancer initiation. Conversely, recombination models report a need for AR in the stroma for cancer initiation to occur (Cunha 1972; Cunha and Chung 1981; Cunha, et al. 2003; Hayward, et al. 2001; Ricke, et al. 2012). Here, proteins released under the regulation of AR in the surrounding stroma act on epithelial cells, not causing cancer initiation *per se* but promoting the initiation process. The role of AR in the stroma remains important in advanced cancer, but changes to a protective role as its expression is inversely associated with clinical outcomes (Leach, et al. 2015; Li, et al. 2008; Ricciardelli, et al. 2005; Wikstrom, et al. 2009).

In a review by Tamburrino et al, several studies were evaluated for correlation between AR expression in the primary tumour and patient outcome (Table 1). In this review,

few studies showed a positive correlation between AR expression and outcome, whilst a majority found no significant association (Tamburrino, et al. 2012). However these studies were only looking at WT-AR expression: AR mutations and alteration may mean that AR has more of an effect than these expression data may show, particularly as AR mutations are known to alter proliferation, treatment tolerance, and aggressiveness (Tepper, et al. 2002) (Sun, et al. 2006). AR somatic mutations in prostate cancer are mostly associated with gains in function/activity, and appear to be selected for during progression as they are detected in CRPC but not in untreated and localised prostate cancer (Grasso, et al. 2012). These somatic point mutations can cause alterations to the AR structure to mimic an AR activated by ligand, or allow altered coregulation interaction, such that binding to antagonists can actually stimulate activity (Bohl, et al. 2005; Bohl, et al. 2007; Brooke and Bevan 2009; Joseph, et al. 2013).

Other forms of altered AR found in prostate tumours are splice variants, truncated forms of AR which lack LBD but with just the NTD and DBD are transcriptionally active independent of the presence or absence of ligand or antagonists (Dehm and Tindall 2011). This ligand-independence makes truncated AR variants potentially very important to disease progression and patient treatment response. Experiments with siRNA have confirmed that truncated AR is a result of alternative splicing and not due to modification of post transcribed mRNA or protein (Dehm, et al. 2008). The presence of different truncated AR variants has been confirmed in multiple cell lines, as well as xenograft models, mouse models, and patients (Brand and Dehm 2013; Dehm and Tindall 2011; Guo, et al. 2009; Hu, et al. 2009; Nyquist and Dehm 2013; Sun, et al. 2010). Importantly AR-Vs have activity similar to activated full length AR in both reporter arrays and RT-qPCR analysis of classically AR-regulated genes (Chen, et al. 2012a; Dehm et al. 2008; Guo et al. 2009). Additionally, global genomic analysis has identified that the AR-V transcriptome is largely the same as WT-full length AR, with only a small proportion of AR-V specificity, which interestingly seems to include genes involved in cell cycle processes (Hu, et al. 2012; Li, et al. 2013; Nyquist and Dehm 2013). Clinically, the expression of AR-V appears to increase after anti-androgen therapy, particularly in metastatic lesions (Dehm et al. 2008; Hornberg, et al. 2011; Hu et al. 2009; Hu et al. 2012; Watson, et al. 2010). These have largely been identified at a RNA level, as robust antibodies only exist for ARV-7 subtype, the protein of which has been confirmed in CRPC patient samples by multiple reports (Guo et al. 2009; Hu et al. 2012; McGrath, et al. 2013). It has long been known that overall AR levels increase under the same circumstances,

and indeed the ratio between AR-Vs and full-length seems to remain fairly constant, thus whether increased expression of AR-V results from the selective pressure of treatment or is simply a consequence of overall increased AR expression is not yet clear.

Estrogen receptors (ERα or NR3A1 and ERß or NR3A2)

The roles of estrogens and androgens have traditionally been viewed as being in opposition and so given the importance of androgen signalling in prostate there is little wonder that over recent years there has been a renewed interest in attempting to understand the balance of androgenic and estrogenic signalling in prostate biology, and thus the importance of ER biology (Grubisha, et al. 2012). There are two major types of estrogen receptors (ERs), ERα and ERβ, encoded by separate genes (ESR1 and ESR2)(Yeh, et al. 2014). The expression and location of these two receptors within the prostate differ. ERα is mainly expressed in the stromal cells within the non-malignant human prostate but can occasionally also be found in the basal-epithelial cells, while ERβ appears to be mainly confined to the basal-epithelial cells (Lau, et al. 2000; Leav, et al. 2001; Royuela, et al. 2001). These two receptors play significantly different roles within the prostate tissue, with ERα mediating the adverse effects upon stimulation, such as aberrant proliferation, inflammation and pre-malignant pathology. Conversely the prevailing ER subtype within the prostate is ERβ, which appears to mediate the beneficial effects of estrogen stimulation by acting in a putative protective role against carcinogenesis (Ellem and Risbridger 2010; Linja, et al. 2003; Risbridger, et al. 2007).

Animal models have been used to elucidate the roles estrogen receptors and estrogen may play in prostate carcinogenesis. The local paracrine conversion of androgens to estrogens is driven by the aromatase enzyme, expressed in the stromal cells of the normal prostate (Risbridger et al. 2007). In studies using the aromatase knockout mouse model, it has been shown that the mice fail to develop prostate cancer despite having lifelong elevated levels of androgens, but abnormal prostate biology is triggered by the administration of synthetic estrogens early in development (Grubisha and DeFranco 2013; McPherson, et al. 2001). To determine which estrogen receptor may be responsible for the development of prostate cancer in these mice, the ERα and β knockout models were studied. The prostates from the ER beta-knockout mice underwent biochemical and histological carcinogenesis, similar to observations seen in the ER wild-type mice. However the prostates from the ER alpha-knockout mice remained free from any pathology (Ricke, et al. 2008). Therefore these

studies suggested that not only is local production of estrogen within the prostate a significant factor in prostate carcinogenesis but that this adverse effect is mediated through ERα, highlighting the possibility of antagonizing ERα, but not ERβ as a future therapy.

Both ERα and ERβ have been reported in samples obtained from prostate cancer patients, but the relative levels in different stages of prostate cancer remain contentious (Table 1). ERα is abundantly expressed in normal and tumour stroma, where the levels decrease during prostate cancer progression potentially indicating a protective role (Daniels, et al. 2014), it is however unclear if this is an effect of cancer progression or causative factor in cancer progression. Aside from in the stroma, there are differing reports about whether it is expressed in epithelial prostate cancer cells. Many studies report negligible ERα staining in prostate cancer cells using immunohistochemistry. This could be due to an under-representation of high- grade samples because other studies showed that ERα expression in prostate cancer cells is significantly associated with high Gleason score and poor patient survival (Takizawa, et al. 2015). Using immunohistochemical staining and in situ hybridisation studies of prostate cancer tissues, Bonkhoff *et al.* demonstrated the presence of ERα in both premalignant lesions and prostatic adenocarcinoma. ERα mRNA and protein expression was seen in 28% and 11% of high-grade prostatic intraepithelial neoplasia cases evaluated. Focal ERα immunoreactivity was detected in a minority of low- to intermediate-grade adenocarcinomas. High-grade primary tumours (Gleason grade 4 and 5) revealed ERα protein expression in 43% and 62% respectively of cases. The most significant ERα gene expression, at mRNA and protein levels, was observed in hormone refractory tumours and metastatic lesions, including lymph node and bone metastases (Bonkhoff, et al. 1999). Furic et al (Takizawa et al. 2015) selected a cohort of tumours of Gleason grade 6 and 9 to ensure that both low and high grade tumours were represented; they found ERα was expressed in 48% of Gleason score 9 specimens but no ERα was observed in the Gleason score 6 tumours, thus confirming the earlier findings of Bonkhoff et al. Another recent study reported that 15% of locally invasive tumours, spanning Gleason score 6 to 10, expressed ERα and that it was significantly associated with biochemical recurrence, decreased progression free survival and poor overall survival (Takizawa et al. 2015). A further study has reported that the expression of ERα and aromatase (CYP19) with the R264C polymorphism, a missense SNP located on the CYP19A1 locus, has been shown to result in shorter progression-free survival and an increased risk of developing CRPC in a study of 115 men treated with docetaxel. Taken together, these observations support the hypothesis that ERα can act as an oncogene by

mediating the adverse effects of estrogen in the prostate (Nelson, et al. 2014).

The expression of ERβ is variable, it is normally expressed at high levels in the epithelium of the prostate and also in the stroma but its expression is decreased or lost in prostate cancer samples (Daniels et al. 2014; Risbridger et al. 2007). A study by Horvath et al assessed five normal prostates from organ donors and 159 radical prostatectomy specimens from patients with clinically localized prostate cancer for ERβ expression using immunohistochemistry. In the five normal prostates strong ERβ-nuclear staining was observed in over 95% of the epithelium and 35% of the stromal cells. However the number of ERβ-positive cases declined to 24.2% (38/157) in epithelial hyperplasia adjacent to carcinoma and 11.3% (18/159) in prostate cancer. ERβ-positivity was related to decreased relapse-free survival (log-rank $P = 0.04$). Thus, loss of ERβ expression is associated with progression from normal prostate epithelium to prostate cancer, whereas those cancers that retained ERβ expression were associated with a higher rate of recurrence (Horvath, et al. 2001). Conversely, a further recent study by Zellweger et al evaluated the protein expression profile of ERβ in a tissue microarray consisting of 107 hormone-naïve (HN) and 101 castration-resistant (CR) prostate cancer samples. They showed that higher ERβ expression in the HN prostate cancers is associated with a higher Gleason grade and increased proliferation. More than 50% of the patients in the matched patient cohort showed a significant increase in ERβ expression after progressing to castration resistance (Zellweger, et al. 2013). In contrast, data from this study appears to advocate that ERβ plays a more tumour-promoting role, at least in the context of progression to castration resistance.

Understanding the primary mechanisms and potential role of ERβ in prostate carcinogenesis is currently difficult due to the variability reported in ERβ expression in differing grades and stages of prostate cancer (Table 1). Increasing evidence has emerged that the existence of ERβ isoforms may play a role. At least five isoforms of ERβ have been identified in humans; ERβ1, ERβ 2, ERβ4, and ERβ5 isoforms can be found in various cell types in the normal prostate and are differentially expressed during the prostate cell cycle (Christoforou, et al. 2014). In a study of 144 patients with long-term follow up, the co-expression of ERβ2 and ERβ5 was shown to be an independent prognostic marker for biochemical relapse, postoperative metastasis and time to metastasis following radical prostatectomy for localized prostate cancer (Leung, et al. 2010). The dominant isoform in prostate cancer is ERβ2, however its mechanism of action remains unclear as it lacks the

LBD, it appears to act as a transcriptional repressor of ERβ1, thus disabling its usual, protective effects.

Progesterone receptor (PR or NR3C3)

The role of PR in prostate cancer is somewhat controversial. In the surrounding stroma, PR expression is very apparent and indisputable, however its expression in the benign and malignant epithelium is varied (Bonkhoff, et al. 2001; Brolin, et al. 1992; Latil, et al. 2001; Luetjens, et al. 2006; Yu, et al. 2013). There have been reports of PR expression in primary prostate cancer and metastatic samples, and an association with ER levels – unsurprising since the PR gene is an ER target (Bonkhoff et al. 2001; Hiramatsu, et al. 1996; Hobisch, et al. 1997; Latil et al. 2001). There is also a recent report associating high PR expression in cancer cells with reduced clinical failure-free survival in a cohort of over 500 patients (Table 1)(Grindstad, et al. 2015).

Progesterone receptor exists in 2 isoforms – PR-A and the longer PR-B, which has an expanded N-terminal domain (Kastner, et al. 1990). In the stroma, both isoforms are much more prominent than in the epithelia. Here progesterone inhibits stromal cell proliferation and alters differentiation towards an activated phenotype (Yu et al. 2013; Yu, et al. 2015). PR activity in the stroma also regulates the secretion of factors which slightly suppress tumour proliferation, but also dramatically inhibits cancer cell motility (Yu, et al. 2014). Despite this conflict over expression levels, there is evidence to suggest that PR antagonists may have therapeutic responses indicating that PR signalling may actually be an important carcinogenic process in prostate cancer (Check, et al. 2007; Chen, et al. 2016).

Glucocorticoid Receptor (GR or NR3C1)

Glucocorticoids, such as cortisol, produced by the adrenal glands, bind to and activate the glucocorticoid receptor (GR) which is almost ubiquitously expressed throughout the body. GR is similar to AR in that it is stably maintained in the cytoplasm until activation when it translocates to the nucleus. Glucocorticoids are administered routinely in prostate cancer (as in a plethora of other diseases and conditions) due to their anti-inflammatory effects. Their

use is associated with improved patient quality of life scores, and reduced serum PSA levels (Coutinho and Chapman 2011; Kassi and Moutsatsou 2011; Rhen and Cidlowski 2005). However a number of studies have queried the use of glucocorticoids, as posthoc analyses of trial cohorts suggest that the stimulation of GR signalling may have a negative effect on outcomes for patients with prostate cancer (Montgomery, et al. 2014; Montgomery, et al. 2015; Shen and Ye 2012; Shen, et al. 2012). In these studies, analysis of patients in clinical arms which received glucocorticoids have significantly worse outcomes than patients that did not. There have also been reports linking GR signalling to promotion of resistance to androgen targeted therapy (Isikbay, et al. 2014; Song, et al. 2014). There have been a number of suggested explanations for this. It is possible that the presence of increased glucocorticoids in the serum, and the absence of androgen, selects for "promiscuous" AR variants with mutations in the LBD allowing their activation by glucocorticoids (Lorente and De Bono 2014; Lorente, et al. 2014). Androgens are also known to down regulate GR expression, so androgen ablation therapy can actually increase GR expression, providing greater potential for GR signalling (Arora, et al. 2013; Ferraldeschi and de Bono 2013; Xia, et al. 2015). Also, GR can substitute for AR signalling. The two receptors can bind to the same sequence-specific response elements (Helsen, et al. 2012) and many AR-regulated genes are also regulated by GR, indeed, GR is reported to induce KLK3 and TMPRSS2 expression (Arora et al. 2013; Isikbay et al. 2014; Tomlins, et al. 2006; Tran, et al. 2009). Importantly it has also been reported that the use of a GR antagonist can sensitise prostate cancer to docetaxel therapy (Kroon, et al. 2016).

Mineralocorticoid receptor (MR or NR3C2)

The mineralocorticoid receptor (MR) is the cognate receptor for mineralocorticoids, such as aldosterone and deoxycorticosterone, but also binds with high affinity to glucocorticoids such as cortisol. Glucocorticoids are commonly used in treatment of castrate resistant prostate cancer (Fakih, et al. 2002). Corticoid steroids are used in prostate cancer patients to restore sensitivity to abiraterone in resistant patients. In a recent retrospective analysis of patients in COU-AA-301 study, corticoids were actually associated with lower PSA but also poor overall survival (Montgomery et al. 2015). Interestingly, increases in serum mineralocorticoids is actually a reported response to abiraterone treatment creating a resistance loop. To complicate matters further, agents used to inhibit the excess of

mineralocorticoids can actually activate wild-type and mutant AR (Richards, et al. 2012). However in a study of 250 men with prostate cancer, serum cortisol levels were reportedly higher in locally advanced prostate cancer (Heracek, et al. 2007). Mineralocorticoids are also reported to inhibit AR function by inhibiting androgen induced conformational changes (Kim, et al. 2014). MR is expressed in multiple prostate cancer cell lines regardless of AR status and appears to be regulated by inflammatory cytokines (Dovio, et al. 2009). Inflammatory responses are highly involved in prostate cancer progression, so subsequent changes in MR expression from inflammatory cytokines may be hypothesised to be involved in carcinogenesis. However much more work seems to be needed to elucidate the roles of MR in prostate cancer.

Other Liganded Receptors

Vitamin D receptor (VDR or NR1I1)

Epidemiological data has shown an inverse correlation between lethal prostate cancer and geographical location, where the position of patient occupancy is indicative of sun light exposure and thus vitamin D (OHD) levels (Nair-Shalliker, et al. 2012; Schwartz and Hanchette 2006). Vitamin D deficiency has also been associated with increased risk of being diagnosed with prostate cancer (Murphy, et al. 2014). Indeed low serum vitamin D levels are also associated with higher Gleason score and extra-prostatic extension (Nyame, et al. 2016). In mice models, dietary OHD is reported to have anticancer activity (Swami, et al. 2012), and human prospective studies find an inverse correlation between serum OHD levels and reduced risk of lethal prostate cancer (Shui, et al. 2012). Furthermore, in humans, OHD treatment can reduce ki67 staining in prostate tumours (Wagner, et al. 2013). In a phase 1 clinical trial, VDR agonist combined with docetaxel reduced PSA levels in patients with metastatic disease (Medioni, et al. 2014). However, a systematic review by Buttigliero (Buttigliero, et al. 2011), failed to demonstrate a benefit for prostate cancer patients. Similarly, in a meta-analysis, VDR expression had no significant effect on outcomes (Theodoratou, et al. 2014). However, there is also a potential importance for VDR polymorphisms in prostate cancer patients, of which a number have been associated with disease progression and lethality (Gandini, et al. 2014; Shui et al. 2012).

In vitro, VDR has anti-proliferative and pro-differentiation effects on prostate cancer cells. VDR also appears to regulate expression of microRNAs (miRs), and appears to do so in

a cell line-dependent manner, indicating that perhaps VDR regulation of miRs may change during cancer progression (Singh, et al. 2015).

VDR is expressed in BPH-associated and cancer-associated stroma (Hidalgo, et al. 2007). VDR is active in both conditions, although coregulator recruitment is altered in the cancerous conditions (Hidalgo, et al. 2011). Interestingly, VDR activity in the prostate cancer stroma shares a number of coregulators with AR, and is able to regulate the expression of genes which are capable of altering cancer cell proliferation (Solomon, et al. 2014).

Thyroid receptors (THRA/B or NR1A1/2)

Thyroid hormone receptors (THRs) are ubiquitously expressed in human prostate epithelial and cancer cell lines and tissue (Hsieh and Juang 2005). The ligands for THRs, T3 and T4, are significantly higher in the serum of patients with prostate cancer compared to those with BPH and normal control individuals (208 prostate cancer patients, 20 BPH, 27 control). Importantly there was also an association between high T3 levels and cancers designated as high risk, as well as clinical stage and recurrence (Lehrer, et al. 2001). In a smaller study of 68 patients, higher serum thyroid hormone levels associated with patients at high risk of cancer progression (Mondul, et al. 2012). In vitro, T3 and T4 through THRs inhibit prostate cancer cell proliferation by down regulating anti-proliferative genes (Hsieh and Juang 2005; Tsui, et al. 2008). THR signalling has also been suggested to have a pro-tumourigenetic effect through the regulation of cytokines (Ding, et al. 2015a; Ding, et al. 2015b) as well as regulation of the proto-oncogene c-FOS (Martinez, et al. 2000). Furthermore, THR signalling is also reported to affect AR status in rodent prostate models (Aruldhas, et al. 2010). Whilst the mechanism by which THR signalling affects prostate cancer remains unclear, rodent studies which utilized agents to inhibit thyroid hormone production, thus stopping THR signalling, reported reduced PC3 xenograft tumour growth (Theodossiou and Schwarzenberger 2000; Theodossiou, et al. 1999).

Retinoic Acid and Retinoid X Receptors (RARs and RXRs)

Retinoic acid receptors and retinoid X receptors are activated by metabolites of vitamin A or retinol (all-trans retinoic acid binds/activates RARs and 9-cis retinoic acid RXRs) and together when transported to the nucleus, they form heterodimers to influence gene

transcription. Specifically they bind to retinoic acid response elements (RAREs) at gene promoters, also through post translational modifications they interact with different coregulators to produce different genetic effects (Al Tanoury, et al. 2013). In a recent analysis of 15 studies, totalling 11, 239 cases of prostate cancer, the level of retinol was positively associated with overall prostate cancer risk, with high levels of retinol increasing risk by 13%, but not associating with stage or grade (Key, et al. 2015). This is surprising considering, retinoids have traditionally been viewed as anti-oncogenic (Willett 1985; Wolbach and Howe 1925, 1933) and used in a number of cancer treatment settings (di Masi, et al. 2015).

Mechanistic studies would also suggest that RARs and RXRs have beneficial/ anti-cancer roles in prostate cancer. In both types of receptors there are three subtypes, the alpha and gamma forms of both RAR and RXR appear to be prevalent in prostate cancer tissue, whilst the beta forms have minimal expression (Kikugawa, et al. 2000; Lotan, et al. 2000)(Table 1), although RARβ and RXRβ expression could be further reduced through ADT therapy. Whilst RARα/γ and RARα/γ are highly expressed, they don't appear to change with carcinogenesis or progression (Kikugawa et al. 2000; Lotan et al. 2000; Rogenhofer, et al. 2012). The function of RARs and RXRS appear to be controlling cell stem-ness and differentiation (Gudas 2013). A number of reports have also noted an up regulation in apoptosis caused by activation of RARs and RXRs, specifically upregulating Bax and other apoptotic genes, as well as down regulating genes that drive proliferation such as cyclin D (Sha, et al. 2013). These effects have been recapitulated using synthetic compounds to enhance cell death in cancer cells (Chen, et al. 2015). This also has led to several clinical trials currently under way investigating the use of retinoids (Tretinoin, Isotretinoin, B-carotene, Fenretinide) to treat prostate cancer (di Masi et al. 2015).

Hepatocyte Nuclear Factor (HNF4α/γ or NR2A1/2)

There are two isoforms of hepatocyte nuclear factors, HNF4α and HNF4γ. This nuclear receptor was originally classed as an orphan receptor, but it was subsequently found that linoleic acid can endogenously bind to the receptor (Yuan, et al. 2009). Men with higher linoleic acid have reduced risk of low grade prostate cancer and prostate cancer overall in the SELECT trial (Brasky, et al. 2013), which may indicate a role for HNF4s in supressing cancer development. However the role of serum linoleic acid in prostate cancer is

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controversial, as there are conflicting reports on the relative association of serum levels and cancer development and progression (Attar-Bashi, et al. 2004a; Attar-Bashi, et al. 2004b). There is also uncertainty whether serum levels reflect levels in prostate, and actual HNF4 activity.

In a study looking at the early stages of prostate development, rats exposed to bisphenol A (BPA; a carcinogenic in humans (Prins, et al. 2014)) and testosterone exhibited induction of hyperplasia, PIN, and marked immune responses, and these changes were found to be associated with significantly increased levels of HNF4α (Lam, et al. 2016).

HNF4 polymorphism is significantly associated with higher serum PSA levels in prostate cancer patients but not with lymph node metastasis, although a trend was reported (Reyes-Hernandez, et al. 2014). It is reported to also have a role in AR signalling, specifically binding near AR and maybe acting as a pioneer factor (Pihlajamaa, et al. 2014) but more research is required to elucidate the potential role of HNF4 proteins in AR pathways.

Intriguingly, HNF4 is reported to bind to the promoter region of CYP7A1 and enhance transcription, both *in vitro* and *in vivo* (Kir, et al. 2012; Stroup and Chiang 2000). CYP7A1 is an enzyme involved in the cholesterol metabolism, most commonly CYP7A1 activity is measured in the liver and intestine, but it is noted to be expressed in human tissue involved in steroidal genesis and activity, such as the prostate (Wu, et al. 1999). CYP7A1 is noted for metabolism of cholesterol to bile acids, the action of the enzyme in prostate is yet to be elucidated, but it could be hypothesised that the increased HNF4 activity driving up regulation of CYP7A1 could actually be a means of altering cholesterol metabolism away in castrate resistant prostate cancer.

"Metabolic" NRs

Several NRs function as lipid and metabolic intermediate sensors, responding to dietary lipids and their metabolites. Although these do not constitute a distinct group in the evolutionary sense, and include both liganded and orphan receptors, they are discussed here as a functional subgroup. Although these are the best-characterised to have metabolic effects, other NRs discussed elsewhere can of course also impact upon metabolic pathways. The fact that several NRs with key roles in metabolism also appear to be associated with prostate cancer

progression is intriguing given the association between prostate cancer, particularly lethal disease, and factors such as obesity/BMI, cholesterol metabolism and metabolic syndrome (Giovannucci, et al. 2007; Moller, et al. 2016; Stopsack, et al. 2016).

Peroxisome Proliferator-Activated Receptors (PPARs or NR1C1/2/3)

There are three peroxisome proliferator-activated receptor family members, PPARα, PPARδ, PPARγ that act as fatty acid sensors (Desvergne and Wahli 1999). All three are expressed in prostrate and prostate cancer tissue (Kroll, et al. 2000; Mueller, et al. 2000). PPARα and PPARδ are highly expressed in PIN, BPH, and prostate cancer, but only PPARγ expression is dramatically increased in prostate cancer (Segawa, et al. 2002). Furthermore PPARγ expression is significantly higher in advanced prostate cancer, correlating with Gleason score and shorter prostate cancer specific survival time (Forootan, et al. 2014; Rogenhofer et al. 2012).

All three can form heterodimers with RXR and LXR (Ferre 2004; Tan, et al. 2005; Yang, et al. 2012) and PPARγ can inhibit AR action (Yang, et al. 2007). PPAR action can also be disrupted by NCOR1, similar to AR (Battaglia, et al. 2010). PPARs can mediate apoptosis and proliferation as well as prostate cancer cell differentiation (Koeffler 2003; Nagata, et al. 2008; Wu, et al. 2016b). PPARs have also been reported to alter prostate cancer motility by regulating the CXCR4/CXCL12 axis (Qin, et al. 2014). The action of PPAR also have benefit in adding response to chemotherapy, as treating with PPAR ligands appears to increase apoptosis (Koeffler 2003). Lastly it has been reported that in prostate cancer tissue, PPARs can lead to upregulation of VEGF thus enhancing tumour vascularisation and growth (Forootan, et al. 2016; Haslmayer, et al. 2002). This is quite in conflict with in vitro work and another report which suggest that PPARs inhibit vascularisation (Qin et al. 2014), thus further work is needed to elaborate the beneficial or harmful role of PPARs in prostate cancer development and progression.

Liver X Receptors (LXRβ/α or NR1H2/3)

Liver X Receptors (LXRs) are two closely related transcription factors initially isolated in the liver and activated by endogenous cholesterol derivatives, the oxysterols (de Boussac, et al. 2013). LXRβ is ubiquitously expressed whereas LXRα has a more limited distribution and is

found mainly in metabolic tissues. LXRs function as heterodimers with RXR and are involved in retinoid signaling (Lin and Gustafsson 2015). The study of the LXRs within the prostate cancer field was a result of observations first reported highlighting changes in cholesterol metabolism in cancerous tissues, including early stages of prostate carcinogenesis (Lin and Gustafsson 2015). To date all studies have used cell-line models of prostate cancer (in vitro or in vivo). The synthetic LXR agonist T0901317 is able to inhibit prostate cancer cell proliferation and the formation of tumors in xenograft models (Fukuchi, et al. 2004b), and delay the progression of prostate cancer from androgen-dependent to an androgen-independent state in an *in vivo* progression model (Chuu, et al. 2006). Metabolic targets of LXRs that may be involved in the anti-proliferative effects observed in prostate cancer cells include the cholesterol transporter ATP-binding cassette sub-family A member 1 (ABCA1). Activation of LXR leads to increased expression of its *ABCA1* in prostate cancer cells, while ABCA1 levels decrease during prostate carcinogenesis; if the expression of ABCA1 is disrupted an increase in cell proliferation is observed (Fukuchi, et al. 2004a). In a related study, LXR ligand treatment of prostate cancer cells was shown to increase the expression of cholesterol transporter ABCG1 and to alter cellular membrane lipid raft signaling via the protein kinase AKT1, resulting in increased apoptosis (Pommier, et al. 2010). The activation of LXR has also been shown to lower circulating androgen levels *in vivo* by inducing expression of hydroxysteroid sulfotransferase 2A1, an enzyme essential for the metabolic deactivation of androgens (Lin and Gustafsson 2015). Due to this androgen-dependent prostate regeneration and prostate cancer cell growth is inhibited. The authors therefore propose that LXR-mediated SULT2A1 activation represents a novel mechanism of androgen deprivation, which may have its utility in developing therapies for hormone-dependent prostate cancers (Lee, et al. 2008). In the field of prostate cancer as yet, little is known regarding LXR transcripts and protein expression profiles, especially in clinical cancer samples and clinically relevant model systems, and to date no LXR agonist has been developed specifically for cancer therapeutics (Lin and Gustafsson 2015).

Farnesoid X Receptor (FXR or NR1H4)

FXR acts as a bile acid sensor and was initially isolated in the liver where it plays a critical role regulating bile acid, cholesterol and steroid metabolism. FXR has been reported to be expressed in normal prostate tissue as well as in the prostate cancer cell line LNCaP, where it

was shown that activators of FXR can regulate androgen metabolism and it can also, interestingly, be activated by certain androgen metabolites, suggesting a possible role in eliminating active androgens from the prostate (Kaeding, et al. 2008). A further study reported that FXR expression was significantly decreased in a cohort of 25 human prostate cancer tissues as compared to pair-matched adjacent normal tissues (Liu, et al. 2014). *In vitro* studies also demonstrated that activation or overexpression of FXR inhibited proliferation of the prostate cancer cell line LNCaP. At a molecular level the results from this study revealed that expression of the tumour suppressor gene, PTEN, was upregulated by FXR activation, leading the authors to suggest that the FXR functions as a tumour suppressor in prostate cancer and may provide a novel target (for activation) in treatment.

Pregnane X Receptor (PXR or NR1I2)

Pregnane X receptor, also known as steroid and xenobiotic receptor (SXR) is an orphan nuclear receptor, distinct among NRs due to its broad ligand specificity. PXR binds and responds to a wide spectrum of structurally distinct endobiotic substrates and environmental xenobiotics including food additives, and clinically used drugs such as antibiotics and chemotherapeutics (doxorubicin, taxol). It is expressed in a wide variety of tissues throughout the body where it provides a protective mechanism for critical cells that are sensitive to aberrant levels of such compounds. PXR has been shown to coordinate the detoxification of these compounds by modulating expression of drug metabolizing enzymes such as CYP3A4 (Chen, et al. 2012b; Fujimura, et al. 2012; Kumar, et al. 2010).

The expression of PXR in human prostate tissues has been studied by immunohistochemistry of normal ($n = 19$) and cancerous prostate tissues ($n = 124$). In the cancer, PXR expression was generally elevated compared to the normal tissues, with tumours of Gleason grade 6 presenting with the highest levels of expression. However, when the tumours progressed to a more advanced stage, the expression of PXR tended to be reduced. The human prostate cancer cell lines PC-3, LNCaP and DU145, were also shown to express PXR. Pre-activation of PXR with synthetic ligand SR12813 in PC3 cells led to an enhanced resistance to chemotherapeutic agents, due to the enhanced expression of both CYP3A4 and MDR1. However the down-regulation of PXR using targeted shRNA in PC3 cells resulted in the re-sensitization of these cells to the chemotherapeutic agents. The authors suggest that if activation of human PXR (hPXR) is one of the major underlying mechanisms of drug

resistance in cancer chemotherapy, inhibition of PXR will be a new approach to enhance the clinical efficacy of prostate cancer chemotherapy (Chen, et al. 2007). A further study looking at PXR and CYP3A4 expression in benign (n = 78) and cancerous (n = 106) tissues, obtained by radical prostatectomy, reported that high expression of these correlated with good prognosis and increased survival in prostate cancer patients. This suggests they may be a strong prognostic indicator of favourable outcomes in, and could be a therapeutic target for, prostate cancer (Fujimura et al. 2012).

Orphan Receptors

Orphan receptors are a subgroup of nuclear receptors with no yet identified endogenous ligand. Often classified as constitutively active, several appear to have ubiquitous, endogenous molecules associated permanently with the LBD, i.e. be permanently liganded. This however does not preclude the possibility of modifying their activity using synthetic compounds and small molecules, and so they are potential drug targets in cancer and other diseases. A recent review has covered orphan receptors in prostate cancer in detail (Wu D et al 16), so here we will focus on a small number of prominent receptors which were identified as highly altered in our TCGA analysis.

TLX (aka TLL or NR2E1)

TLX was original investigated in cancer biology due to its very apparent role in brain tumours, however exploration in other cancers such as prostate is limited. Protein expression of TLX is unregulated in higher Gleason grade prostate tumours compared to BPH and lower Gleason score tumours (Wu, et al. 2015). TLX has been reported to have a role in overcoming senescence (oncogene-induced and PTEN-loss-induced) in multiple tumour types including prostate, as it can repress p21 and activate SIRT1, both of which are prominent senescence related genes (Wu et al. 2015). This role in senescence may make TLX an important factor in cancer progression and CRPC, where senescence is thought to be a vital part of tumour resistance to treatment and recurrence, and Wu and coworkers suggest that TLX may promote self-renewal and maintenance of cancer stem cells (Wu, et al. 2016a). Further research into the role of TLX in prostate cancer progression is clearly needed,

especially as in our analysis of TCGA data (Figure 1), TLX is the most frequently altered orphan nuclear receptor in prostate cancer patients.

Estrogen Related Receptors (ERRα/β/γ or ESRR α/β/γ or NR3B1/2/3)

Estrogen related receptors are orphan nuclear receptors with three subtypes ERRα, ERRβ, ERRγ, that are constitutively active without interaction with oestrogen. They do, however, bind to the same response elements as ER (as dimers or monomers), and so there is an overlap and crosstalk between the respective signalling pathways. Of the three subtypes, ERRα and ERRγ are the most consistently and prominently expressed in prostate cancer, cells, tissue, and xenografts at both RNA and protein levels, whilst ERRβ expression is high in normal prostate tissue but lost in cancer (Cheung, et al. 2005). Expression of ERRα is inversely associated with prostate cancer outcome: in a cohort of 106 patients, ERRα expression increased in cancer compared to BPH, and was significantly associated with poor prostate cancer specific survival (Fujimura, et al. 2007). Consequently, ERRα has been reported to be pro-proliferative (Bianco, et al. 2009) whilst also providing protection against hypoxia (Zou, et al. 2014), and increasing prostate cancer cell invasiveness (Tribollet, et al. 2016). ERRα has also been reported to have a role in AR signalling, by binding to AREs independently of AR and promoting gene transcription (Teyssier, et al. 2008). The role of this in prostate cancer is yet to be fully elucidated. As well as modulating steroid receptor (AR and ER) signalling, ERRα may also affect prostate cancer progression by regulating metabolic pathways downstream of the master regulator AMPK (Tennakoon, et al. 2014).

Whilst being present in prostate cancer, expression of ERRγ is slightly lower in cancer compared to benign tissue. In androgen responsive and non-responsive cell lines, ERRγ inhibits proliferation, acting through p21 and p27 (Yu, et al. 2007). Interestingly, ERRγ can be activated by the administration of phytoestrogen equol, a synthetic oestrogen with anti-prostate cancer abilities (Hirvonen, et al. 2011), meaning its anti-proliferative ability could be used clinically.

Despite being the only ERR with no expression in prostate cancer, ERRβ is the only subtype with RNA-seq analysis completed in prostate cancer cell lines. In the DU145 cell line, ERRβ (± the synthetic ligand DY131) regulated genes involved in transcription and translation regulation, cell proliferation, apoptosis regulation, and cellular metabolism (Lu, et al. 2015).

Dosage sensitive sex reversal (DSS/DAX1 or NR0B1)

DAX1 is an unusual orphan nuclear receptor as it has no canonical DBD. Rather than binding to DNA, DAX1 exerts transcriptional effects by binding to and inhibiting the action of other chromatin-bound nuclear receptors such as AR, PR, and ERs, and to other orphan receptors (Agoulnik, et al. 2003; Iyer and McCabe 2004; Yuan, et al. 2001). It has been suggested that the protein-protein interactions between DAX1 and NRs blocks the coactivator binding surfaces thus encouraging recruitment of corepressors instead to target gene promoter regions. It has also been suggested that DAX1 can inhibit dimerization of NRs, notably the AR (Holter, et al. 2002; Iyer and McCabe 2004). Unfortunately, there is limited research for DAX1 expression in prostate cancer but the balance points to reduced DAX1 being associated with prostate cancer progression. It is reported to be high in normal prostate epithelial cells but reduced in BPH (Agoulnik et al. 2003; Holter et al. 2002). Nuclear expression of DAX1 is also reported to be reduced with increasing Gleason grade (Nakamura, et al. 2009a). However in the same report, normal tissue had no detectable DAX1 expression. There is also limited in vitro data, as while mRNA is expressed in primary epithelial cancer cells, it is not expressed in investigated cell lines (Lee, et al. 2010). Intriguingly, DAX1 is a target of the putative prostate cancer oncomiR miR-181, supporting a role for DAX1 in inhibiting prostate carcinogenesis (Tong, et al. 2014).

Short Heterodimeric Partner (SHP or NR0B2)

Like its close orphan receptor relative, DAX1, SHP doesn't have a DBD and interacts with other NRs to repress gene transcription (Jouravel, et al. 2007; Zhang, et al. 2000). It appears to interfere with coregulator interaction similarly to DAX1, but it can also inhibit NR binding to DNA (Zhang, et al. 2010). No human tissue expression data for SHP is available, but in vitro work suggests that SHP levels are higher in non-malignant prostate cell lines, and absent or low in prostate cancer cell lines, supporting a role in regulating proliferation and apoptosis (Dawson, et al. 2007; Xiao, et al. 2012).

Retinoic acid receptor-related orphan receptor (ROR α/β/γ or NR1F1-3)

Three isoforms (RORα, RORβ, RORγ) encoded by three genes (RORA, RORB, RORG) and uniquely binding as monomers to DNA at ROREs (Jetten 2009), RORs interact with both coactivators and corepressors to affect gene transcription (Jetten 2009). RORα has been reported in vitro to affect proliferation and differentiation of DU145 cells (Moretti, et al. 2001). It also been reported to reduce the invasiveness of prostate cancer cells (Moretti, et al. 2002). RORγ has been reported to be overexpressed in CRPC and to upregulate AR expression by promoting recruitment of the coactivators NCOA1 and NCOA3 to AR gene promoters (Wang, et al. 2016). Importantly, targeting RORγ was also able to partially inhibit prostate cancer growth and progression. There is limited data on RORs in prostate cancer, but just based on these few reports and TCGA data it would appear they are worthy of future research to dissect their role and therapeutic potential in prostate cancer.

Nuclear Receptor Coregulator in Prostate Cancer

Coregulators are accessory proteins which do not bind DNA directly but interact with NRs to either enhance (coactivators) or inhibit (corepressors) their activity. Coregulators can affect NR activity in two main ways. First, they can alter chromatin compaction and thus recruitment of transcription machinery - via altering histone modifications (acetylation, methylation, and sumolyation). Secondly, they can directly affect NR activity by influencing receptor stability, ligand binding, intracellular trafficking, and interaction with other coregulators. Coregulators either possess the appropriate enzymatic activity to make these alterations or can recruit other proteins that do. The activity and scope of NR coregulators has been reviewed in greater depth elsewhere (Chmelar et al. 2007; Gao, et al. 2002; Lonard and O'Malley 2012) but it is important to note that, while the majority identified appear to interact with multiple NRs, their effects and potency of coregulators, whether they act as a coactivator or corepressor, appear to be gene specific (Leach, et al. 2014; Yang, et al. 2000). Mutations in NRs can affect affect recruitment and activity of coregulators (Chen, et al. 2005; Duff and McEwan 2005; Prekovic, et al. 2016). Furthermore, there are also reports of mutations in the coregulators themselves which also alteres their activity in prostate cancer (Chmelar et al. 2007; Jehle, et al. 2014).

Similarly to the NRs themselves, coregulators are also reported as having altered expression in different stages of prostate carcinogenesis (Heemers, et al. 2010). For instance, overexpression of coactivators such FOXA1 and NCOA1, amongst others, are noted to

increase AR activity in prostate cancer and CRPC while loss of the corepressor NCOA4 is noted to correlate with cancer progression (Wyatt and Gleave 2015). Therapies have also been reported to alter coregulator expression and this has been suggested to be an adaptive response by the tumour to increase NR activity when hormone levels are low (Agoulnik, et al. 2006). Therapy has been reported to alter the type of corergulators present, for example mesenchymal-associated coregulator Hic-5 is upregulated during ADT (Li, et al. 2011), which could result in cancer progression via promoting a more mesenchymal phenotype.

As previously mentioned, NRs share coregulators (Robinson and Carroll 2012; Sahu, et al. 2013). The SRC (Steroid Receptor Coactivator) coregulator family interacts in a ligand-dependent manner with all steroid receptors, whilst coregulators such as SMRT/NCOR appear to interact with both steroid receptors and other liganded receptors, and CBP/p300 interacts with most NRs (Gao et al. 2002; Walsh, et al. 2012). What is not clear is how coregulators are shared between NRs: whether one type of NR has precedence for a particular coregulator over another NR. This is potentially an important area of research, for as we have noted throughout this review, NR expression changes with cancer, thus loss of an NR may liberate certain coregulators to act in other signalling pathways. Conversely, increasing expression of an NR may sequester coregulators away from other signalling pathways.

Summary and conclusions

There is no doubt that the androgen signaling pathways are key in prostate cancer progression and therapy, Equally there can be little doubt that, effective as androgen ablation and other therapies directed at the AR axis are, options are required for patients who become resistant to such therapies. Within the NR superfamily are a plethora of potential drug targets: the prostate expresses many NRs other than the AR and indeed some, such as the GR and ER, have been drug targets in prostate cancer for decades. Others are emerging as strong drug target candidates, either due to their association with AR signaling or in their own right. Many such have roles in metabolic processes, highlighting the attractive prospect of using agents already in clinical development for metabolic disorders to treat both prostate cancer and associated comorbidities. Paradoxically, as other NRs are beginning to enter the prostate cancer stage, the AR itself is coming to the fore in certain other malignancies, most notably breast cancer where it has prognostic value in ER-positive disease and may prove an effective

drug target in the intractable triple-negative subtype (Barton, et al. 2015; Fioretti, et al. 2014; Hickey, et al. 2012). Overall, the NR superfamily represents a rich source of drug targets in prostate and other cancers, and targeting multiple NRs either sequentially or in combination will provide further treatment options and improve prospects for patients whose disease is or has become refractory to conventional therapies.

Conflict of interest

The authors have no conflicts to disclose

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Figure Legends

Figure 1: Schematic diagrams of nuclear receptor structures and DNA binding. A) representative images of different nuclear receptor (NR) types, comparing their overall size and highlighting the amino, N-terminal terminal domain (NTD), the DNA binding domain (DBD), and ligand binding domain (LBD). The AR is used as an example to highlight these regions, as well as the AF1 and AF2 sites. B) NRs interact with DNA in pairs, with either the same NR (homodimer) or another NR (heterodimer), or bind singularly as a monomer. Each NR has a specific mode of binding resulting in gene transcription.

Figure 2: Nuclear receptor alterations in prostate cancer. A) list of 48 nuclear receptors (NR) grouped based on their cognate ligands. B)TCGA data of copy number alterations (CNA) of all NRs in prostate cancer samples. C) TCGA data of mutations detected in all NRs in prostate cancer samples. D) Pie chart demonstrating the incidence of mutations and CNAs in NRs for each NR group.

NR	Authors	Specimens	Cohort size	Methods	Effect on prostate cancer outcome
AR	(Takeda, et al. 1996)	Biopsies	62	IHC	Higher AR, better prognosis
	(Segawa, et al. 2001)	Biopsy, RP and TURP	42	IHC	Higher AR, better prognosis
	(Pertschuk, et al. 1995)	Biopsies	90	IHC	Higher AR, better prognosis
	(Sweat, et al. 1999)	RP	197	IHC	Higher AR, better prognosis
	(Inoue, et al. 2005)	RP	52	IHC	Higher AR, worse prognosis
	(Li, et al. 2004)	RP	640	IHC	Higher AR, worse prognosis
	(Henshall, et al. 2001)	RP	96	IHC	Higher AR, worse prognosis
	(Cordon-Cardo, et al. 2007)	RP	340	IHC	Higher AR, biochemical relapse
	(Donovan, et al. 2010)	RP/Biopsy	66	IF	Higher AR, Worse prognosis
	(Rosner, et al. 2007)	RP	115	RT-PCR	Higher AR, prognostic of PSA recurrence
	(Ricciardelli, et al. 2005)	RP	53	IHC	Higher AR, biochemical relapse
	(Noordzij, et al. 1997)	TURP	68	IHC	Not prognostic
	(Rades, et al. 2012)	RP	64	IHC	Not prognostic
	(Sadi and Barrack 1993)	Biopsies	17	IHC	Not prognostic
	(Sterbis, et al. 2008)	RP	121	RT-PCR	Not prognostic
	(Theodoropoulos, et al. 2005)	TURP and RP	81	IHC	Not prognostic
	(Fleischmann, et al. 2011)	RP and metastasis	119	IHC	Not prognostic
	(Minner, et al. 2011)	RP	2805	IHC and RT-PCR	Not prognostic
	(Sweat et al. 1999)	RP	172	IHC	Not prognostic
	(Leach, et al. 2015)	TURP	65	IHC	Not prognostic
	(Qiu, et al. 2008)	RP	232	IHC	No correlation with CP
	(Schatzl, et al. 2003)	Biopsies	39	IHC	Unavailable
	(de Winter, et al. 1990)	RP	26	IHC	Unavailable
	(Gaston, et al. 2003)	RP	50	IHC	Unavailable
	(Ford, et al. 2003)	TURP	24	IHC	Unavailable
ERa	(Bonkhoff, et al. 1999)	RP	49	IHC, ISH	High ERa associates with Gleason and CRPC
	(Takizawa, et al. 2015)	RP	36	IHC	High Era associates with Gleason, biochemical recurrence, worse PCSS
ERb	(Horvath, et al. 2001)	RP	159	IHC	low ERb associates with PCRFS
	(Zellweger, et al. 2013)		208	IHC	high ERb associates with biochemical relapse
PR	(Grindstad, et al. 2015)	RP	535	IHC	High PR, beneficial reduced PCSS

VDR	(Hendrickson, et al. 2011)	RP	841	IHC	prognostic, high VDR reduced risk of lethal prostate cancer
RARα	(Rogenhofer, et al. 2012)	RP + TURP	233	IHC	slight correlation with progression
	(Lotan, et al. 2000)		32	ISH	Not prognostic
RARβ	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	not prognostic
	(Lotan et al. 2000)		32	ISH	Lost in cancer
RARγ	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	not prognostic
	(Lotan et al. 2000)		32	ISH	Not prognostic
RXRα	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	inverse correlation with cancer progression
PPARγ	(Forootan, et al. 2014)	TURP	132	IHC	high PPARγ correlates with Gleason, reduced PCSS
	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	correlates with advanced and CRPC
	(Nakamura, et al. 2009b)		40	IHC	prognostic, inverse correlation with advance prostate cancer stage
PXR	(Chen, et al. 2007)	RP	106	IHC	prognostic, high PXR increased PCSS
	(Fujimura, et al. 2012)	RP	124	IHC	low PXR, higher Gleason
ERRα	(Fujimura, et al. 2007)	RP	106	IHC	prognostic, high ERRa reduced PCSS
DAX1	(Nakamura, et al. 2009a)	RP	40	IHC	inverse correlation with Gleason
FXR	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	not prognostic
LXR	(Rogenhofer et al. 2012)	RP + TURP	233	IHC	not prognostic

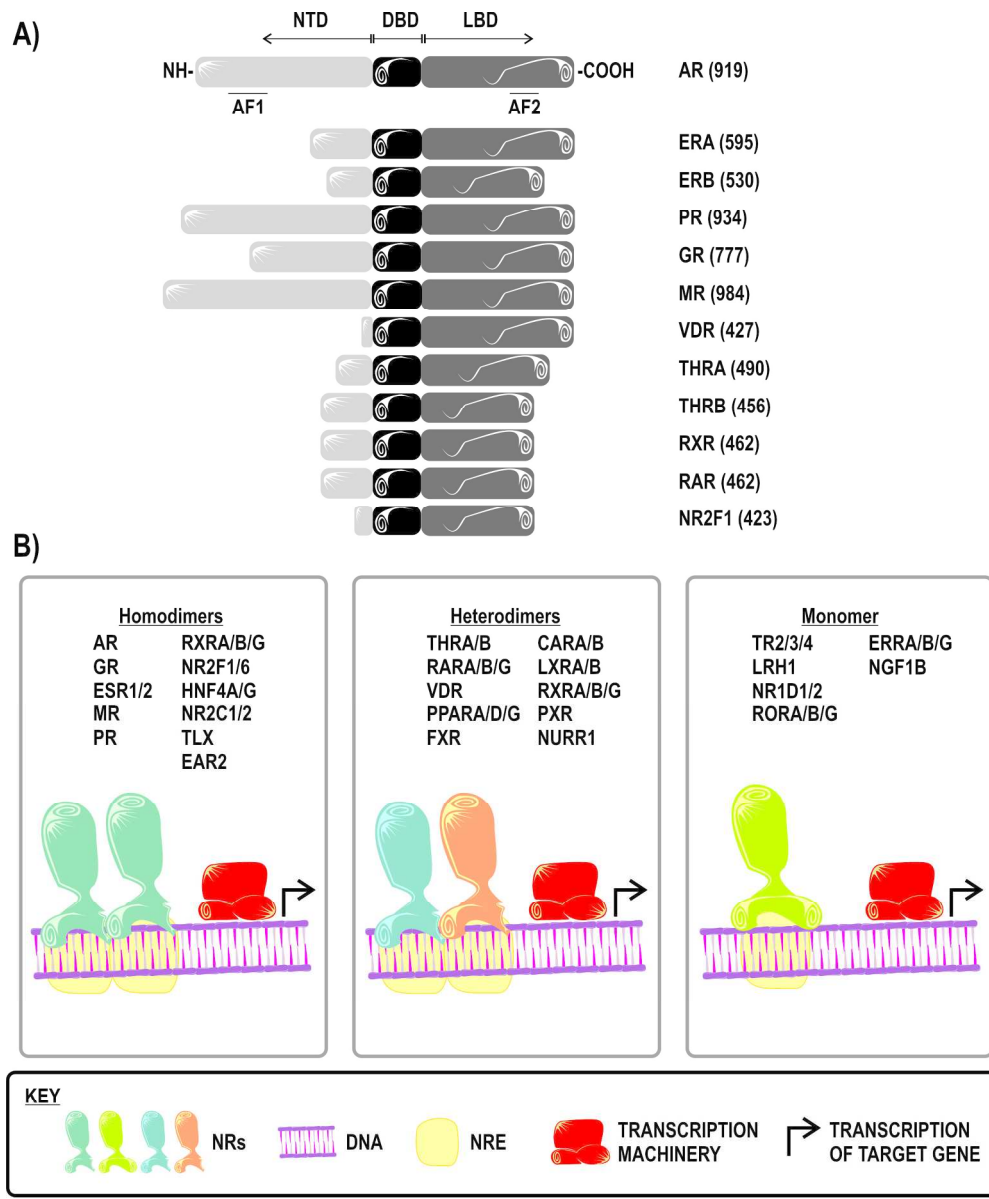**Table 1: NR expression and associations with clinical outcomes.**

Figure 1: Schematic diagrams of nuclear receptor structures and DNA binding. A) representative images of different nuclear receptor (NR) types, comparing their overall size and highlighting the amino, N-terminal terminal domain (NTD), the DNA binding domain (DBD), and ligand binding domain (LBD). The AR is used as an example to highlight these regions, as well as the AF1 and AF2 sites. B) NRs interact with DNA in pairs, with either the same NR (homodimer) or another NR (heterodimer), or bind singularly as a monomer. Each NR has a specific mode of binding resulting in gene transcription.
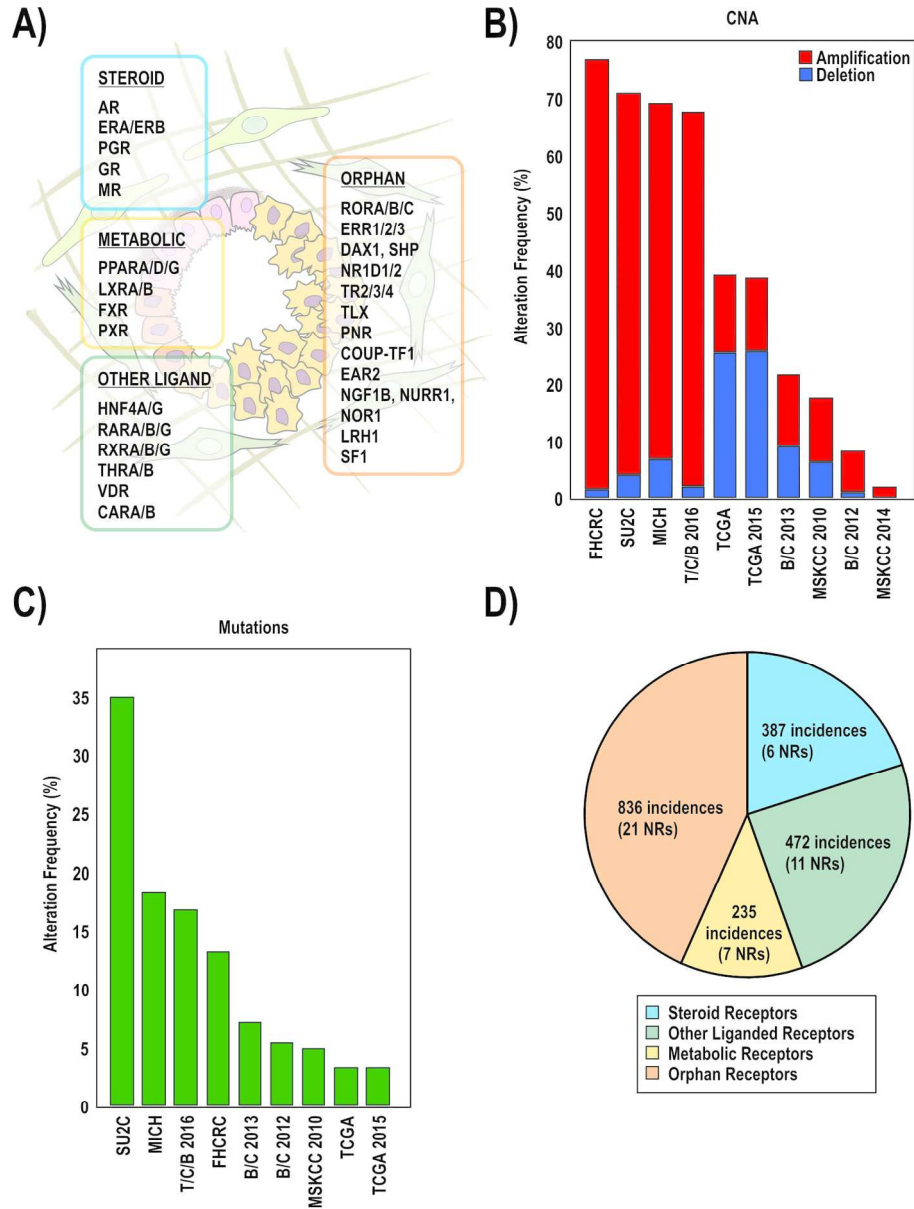
Fig. 1
203x241mm (300 x 300 DPI)

Figure 2: Nuclear receptor alterations in prostate cancer. A) list of 48 nuclear receptors (NR) grouped based on their cognate ligands. B)TCGA data of copy number alterations (CNA) of all NRs in prostate cancer samples. C) TCGA data of mutations detected in all NRs in prostate cancer samples. D) Pie chart demonstrating the incidence of mutations and CNAs in NRs for each NR group.

Fig. 2

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