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Dissecting major signaling pathways in prostate cancer development and progression: Mechanisms and novel therapeutic targets

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Abstract

Prostate cancer (PCa) is the most frequently diagnosed non-cutaneous malignancy and leading cause of cancer mortality in men. At the initial stages, prostate cancer is dependent upon androgens for their growth and hence effectively combated by androgen deprivation therapy (ADT). However, most patients eventually recur with an androgen deprivation-resistant phenotype, referred to as castration-resistant prostate cancer (CRPC), a more aggressive form for which there is no effective therapy presently available. The current review is an attempt to cover and establish an understanding of some major signaling pathways implicated in prostate cancer development and castration-resistance, besides addressing therapeutic strategies that targets the key signaling mechanisms.

Keywords

Prostate cancer; Androgen; Signaling pathways; Castration resistant prostate cancer

1. Introduction

Prostate cancer (PCa) is the most common cancer among men with worldwide detection of more than 8,90,000 new cases and over 2,58,000 deaths each year [1]. Genetic preferences, inflammation, and increased cell proliferation are some of the predeterminant factors for PCa initiation. The occurrence of these processes in the epithelium of normal prostate initiates a cascade of events that lead to the formation of lesions, which can either directly progress to primary PCa or proliferative inflammatory atrophy (PIA) or induce an intermediate stage called prostatic intraepithelial neoplasia (PIN), in which basal cell layers lose their proliferation capacity resulting in increased activity of luminal secretory cells [2].

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Molecular and pathological analysis of human PCa samples and studies with PCa animal models have shown that infectious agents, estrogenic hormones to dietary carcinogens, age, race, genetics and other occupational factors can cause damage to the prostate epithelium and elicit inflammatory responses leading to chronic or recurrent condition of PCa [2].

Androgen deprivation therapy (ADT) via chronic administration of gonadotropin-releasing hormone analogs, anti-androgens or their combination is considered as the standard choice of treatment for men with *de novo* or recurrent metastatic disease [3]. However, most patients invariably relapse and develop castration resistant PCa (CRPC) within 18–24 months despite maintenance of castrate testosterone serum levels, due to amplification or mutations in androgen receptors allowing their activation by progesterone, estrogens and androgen antagonists, generation of alternative splicing variants or to androgen neosynthesis in prostate tumor or adrenals. Besides, a host of molecular alterations also contribute to androgen-independence of PCa cells thereby stimulating disease progression [4,5].

2. *In vitro* and *in vivo* reports signifying the involvement of intracellular signaling cascades in PCa development/progression

The role of AR signaling in PCa development and progression has been well established [6–10]. In addition, several *in vitro* and *in vivo* studies have established the role of other signaling cascades in PCa development and progression. Earlier in 2002, Gasparian et al. [11] reported constitutive activation of nuclear factor kappa- light chain- enhancer of activated B cells (NF-κB) 'survival signaling' pathway in androgen-independent PCa cells. Studies by Zhang et al. demonstrated that activation of NF-κB pathway and subsequent downstream targets contributes to the progression and metastasis of PCa [12]. Huang et al. showed that blockade of NF-κB in human PCa cells is associated with suppression of angiogenesis, invasion, and metastasis [13]. Recently Jin et al. [14] demonstrated that activation of NF-κB signaling increases the expression of androgen receptor splicing variants (ARVs) in PCa cells and converts androgen-sensitive PCa cells to become androgen-insensitive, whereas downregulation of NF-κB signaling inhibits ARV expression and restores responsiveness of CRPC to anti-androgen therapy. In addition to NF-κB, constitutive activation of phosphoinositide-3-kinase/AKT (PI3K/Akt) has also been documented during PCa progression in autochthonous transgenic mouse model [15]. Shukla et al. [16] reported that treatment of human PCa cells LNCaP, PC-3 and DU145 with PI3K pharmacological inhibitor, LY294002, potentially suppressed the invasive properties in each of these cell lines. Chen et al. discussed that epidermal growth factor (EGF) and its receptor (EGFR)/Akt or EGFR/mitogen-activated protein kinase (MAPK) signaling path- ways are critical for maintaining cell survival in PCa [17]. Gan et al. studied the effects of extracellular signal-regulated kinases (ERK) and Akt pathways on EGF-mediated EGFR signaling, trafficking and cell motility in DU145 and PC3 cell lines and confirmed the significance of the EGFR signaling in PCa via ERK as well as Akt-dependent down streaming signaling [18]. Studies with NSK01105, a sorafenib derivative in human PCa cells and xenograft model indicated that this compound inhibited tumor growth and neovascularization by disrupting the EGFR activation [19]. Lorenzo et al. demonstrated the involvement of growth factor receptors of EGFR family in PCa development and

progression to androgen independence [20]. Recent studies by whang et al., on lapatinib, a dual EGFR and HER-2 tyrosine kinase inhibitor [21] gave a new shape to the EGFR signaling concept in the PCa that revealed the potent role of cross-talk of growth factors and their correlation with androgen-mediated development of PCa [22]. Drake et al. experimented on mouse model and projected that elevated tyrosine kinase signaling in advanced PCa [23]. Studies with antagonist of growth hormone inhibitors have also been shown to down-regulate PCa progression via down-regulation and inactivation of Akt and ERK kinases [24]. Deregulation in the expression of downstream effectors of PI3K/and RAS/MAPK pathways, specifically MNK have not only been documented during PCa but are also reported to contribute significantly to PCa growth and development [25–27]. Atala et al. showed that phosphorylation of eukaryotic translation initiation factor 4E (eIF4E), a key downstream target of MNK promotes PCa development and progression [28]. Studies by Feng et al. established that targeting fibroblast growth factor receptor (FGFR) signaling could be a promising approach for treating aggressive PCa [29]. Muñoz-Moreno et al. demonstrated treatment of PC-3 cells with Growth Hormone-Releasing Hormone (GHRH) antagonists significantly decreased the level of gonadotropin-releasing hormone (*GnRH*); vascular endothelial growth factor (VEGF); and hypoxia-inducible factor 1-alpha (HIF-1a) expressions [30]. Yamamoto et al. identified that Wnt5, a critical ligand that activates the β-catenin-independent pathway in Wnt signaling promotes the rapid proliferation and metastasis of PCa [31]. Recently Valkenburg et al. demonstrated that activation of Wnt/β-catenin signaling is sufficient to produce high-grade prostate intraepithelial neoplasia (HGPIN) in hormonally normal mice [32]. Heidegger et al. demonstrated that overexpression of insulin receptor IGF1R promoted tumor growth and enhanced angiogenesis in human PCa cells [33]. Zengerling et al. reported that inhibition of IGF-1R diminishes transcriptional activity of the androgen receptor and its constitutively active, C-terminally truncated counterparts Q640X and AR-V7 via down-regulation of ARΔLBD signaling [34]. Shodeinde et al. disclosed that PCa growth development depend upon activated signal transducer and activator of transcription-3 (STAT3) [35]. Martin et al. showed that STAT3 activation drives CRPC progression via mediating loss of p53, a key tumor repressor [36]. Tyrosine phosphorylation of AR protein by non-receptor tyrosine kinases Src and Ack1 (activated cdc42-associated kinase) has been reported to activate AR even in low androgen environment, thereby promoting CRPC development [37,38].

3. Key molecular pathways promoting PCa development and progression

From the above studies, it is evident that besides AR signaling multiple intracellular signaling circuits play critical roles in the development and progression of PCa (Fig. 1), essentially influencing the transition of PCa cells from androgen dependent to castration resistant (CR) stage. This section summarizes alterations in key intracellular signaling pathways that promote PCa progression and the mechanisms by which they may influence therapeutic action of drugs targeting them.

3.1. Androgen receptor (AR) mediated signaling pathway

The AR signaling is vital for normal functioning of the prostate, and initiation and maintenance of spermatogenesis [6]. AR is a member of the steroid hormone receptor family

of ligand-activated nuclear transcription factors comprising of four distinct functional domains, a poorly conserved N-terminal domain (NTD) with transcriptional activation function; a highly conserved deoxyribonucleic acid (DNA)-binding domain (DBD) liable for DNA binding specificity and dimerization/stabilization of AR-DNA complex; a moderately conserved ligand-binding domain (LBD) that facilitates binding to steroid hormones. A short amino acid sequence called the 'hinge region' separates the LBD from the DBD and also contains part of a bipartite ligand-dependent nuclear localization signal (NLS) for AR nuclear transport [6,39].

Androgenic steroids are 19-carbon steroids with testosterone being the prototype. Testosterone is produced primarily by the testes with a small contribution from the adrenal glands. Testosterone is converted to DHT (highly expressed in prostate and genital tissues) by the action of the cytochrome P450 enzyme, 5α-reductase. Under physiological conditions, both testosterone and DHT can bind to and activate AR signaling.

In the absence of ligand, AR resides primarily in the cytoplasm in association with heat shock proteins (HSPs), cytoskeletal proteins and other chaperones.

Binding of ligand to the AR induces conformational changes in the LBD facilitating intramolecular and intermolecular interaction between N-terminal and C-terminal domains. This subsequently results in AR homo-dimerization, phosphorylation and nuclear translocation. In the nucleus, ligand bound AR binds to specific recognition sequences known as "androgen response elements" (AREs) in the promoter and enhancer regions of target genes along with its coregulators thereby modulating gene expression [6,39].

Deregulated AR signaling is common during PCa development and CRPC progression due to overexpression of AR arising due to amplification/mutations, co-activator and co-repressor modifications, aberrant activation/post-translational modification, altered steroidogenesis, and generation of AR splice variants [40]. Mutations in the AR although rare during initial stages of PCa are common during CRPC. These mutations permit continued androgen-axis activation even in the presence of low levels of androgen in the prostate microenvironment [41,42]. In addition, point mutations in AR besides facilitating increased AR activity in the prostate environment also broaden the ligand pool to which AR responds. In advanced PCa, growth factors such as transforming growth factor β (TGF-β), bone morphogenetic proteins (BMPs), insulin-like growth factor-1 (IGF-1), EGF, VEGF, fibroblast growth factor (FGF), interleukins (ILs), and other cytokines also act to promote synergistic activities of the androgen receptor [43,44]. Besides, more than 200 molecules have been identified as co-activators and co-repressors to the AR. Mutations in the various components of the co-regulator complex have also been reported to improve androgen-stimulated AR activation and disease progression of disease [45,46]. Aberrant activation of AR also occurs via alterations in the steroidogenesis pathways which permits PCa cells to bypass testosterone, and utilize adrenal androgens to generate functionally potent DHT via the 5α-dione pathway [47,48]. ARVs, the splice variants of full length AR generated as a result of alternative splicing such as exon skipping, cryptic exon inclusion, and cryptic splicing donor or acceptor usage also play a crucial role in promoting PCa progression. These splice variants although retain NTD and DBD of full-length AR, lack LBD ensuing in

acquisition of hormone-independent activity to the AR. Besides localization in the nucleus, some AR variants also exhibit exclusive cytoplasmic function that is sufficient enough for transcriptional effects. In addition, ARVs can freely enter the nucleus without association with the Hsp90 chaperone complex [49–51]. Aside from the above described mechanisms that induce changes in the activity of AR, various transcription factors such as the proto-oncogene Myc, c-Jun, Sp1, FOXO3a, lymphoid enhancer binding factor 1 (LEF1), sterol regulatory element-binding proteins (SREBPs), cAMP response element-binding (CREB), NF-κB and twist-1 also have a crucial role in promoting AR expression via gene regulation [52].

3.2. NF-κB signaling

NF-κB is a protein complex that regulates expression of key genes required for innate and adaptive immunity, cell proliferation and survival, and lymphoid organ development. In humans, the NF-κB family comprises of five proteins namely p65 (RelA), RelB, p105/p50 (NF-κB1), p100/p52 (NF-κB2) and c-Rel. These proteins associate with each other to form homo- or heterodimeric complexes that are transcriptionally active. Although 15 different Rel dimer complexes can be made, the p50/65 heterodimer is the most abundant one and occurs in almost all cell types. The Rel proteins are activated by divergent stimuli including pro-inflammatory cytokines, T-and B-cell mitogens, bacteria and lipopolysaccharides, viruses, viral proteins, double stranded RNA, and physical and chemical stressors. In the unstimulated state, NF-κB dimers are retained in the cytosol as inactive proteins bound to IκB (inhibitor of *kappa*) proteins. In the canonical pathway of activation, degradation of the IκB inhibitory protein occurs through phosphorylation at specific serine residues (Ser 177/181 or Ser 176/180) by IκB kinase complex (IKKα or IKKβ). As a consequence, free NF-κB dimer enters the nucleus, binds to κB enhancer sites in the DNA and activates transcription of a wide array of genes participating in the immune and inflammatory response, cell growth, adhesion, metastasis, and apoptosis evasion. In contrast, the non-canonical NF-κB pathway activated by stimuli such as lymphotoxin-β (LTβ) and B cell-activating factor (BAFF) involves IKKα-dependent p100 processing instead of IκB degradation [53,54].

In prostate tumor cells, NF-κB is found frequently stimulated due to augmented levels of receptors such as tumor necrosis factor (TNF) that radically increase IκB degradation [55]. In androgen-independent prostate tumors, NF-κB expression is increased at both mRNA and protein level due to increased IL-6 expression that occurs as a result of constitutive NF-κB activation promoted by signal transduction via NF-κB inducing kinase (NIK) and IKK [56]. NF-κB also targets a transcription regulatory element of the prostate specific antigen PSA, a vital marker for development and progression of PCa [57,58]. NF-κB signaling in PCa cells also correlates with cancer progression, chemoresistance, and PSA recurrence [59]. Reports also indicate that NF-κB activation contributes to soft-tissue or bone metastasis in PCa [60,61]. TNF-α, a proinflammatory cytokine and prototypical NF-κB inducer along with its receptors TNFR1 and TNFR2 are found to be highly expressed in PCa. In Pca cells, amplified TNF-α expression has been correlated with increased proliferation and survival, angiogenesis, metastasis, and resistance to chemotherapeutic agents [62,63]. Recent studies have also demonstrated the existence of cross-talk between NF-κB and AR signaling. NF-

κB expression has been shown to augment with increased AR expression and activity in androgen-independent xenografts. The p65/RelA subunit of NF-κB activity is also reported to increase both the gene and protein expression of AR. Furthermore, p65 of NF-κB could increase endogenous AR expression and its associated downstream target genes enhancing growth and survival in human PCa cells [64,65].

3.3. Growth factor signaling

PCa progression is often interrelated with deregulation of specific growth factors and their respective signaling pathways [66]. Growth factors are of three categories: positive growth factors, which promote growth and proliferation; negative growth factors, which regulate and inhibit cell growth/proliferation and induce apoptosis, and angiogenic growth factors, that provide growth factors necessary to build vascular and oxygen supplies necessary for tissue growth and survival. Growth factor receptors have receptor tyrosine kinase (RTK) activity. Ligand binding to growth factor receptors, triggers signaling pathways resulting in the activation of transcription factors and altered expression of numerous genes responsible for cell growth, proliferation and survival. While IGF-1 and its associated signaling pathway functions as a positive growth-promoting signal transduction pathway, FGF family of growth factors plays the role of both a positive growth factor and an angiogenic growth factor. Transforming growth factor-β (TGF-β) functions as a negative growth factor thereby regulating cell differentiation and proliferation [66,67]. Table 1 summarizes the role of various growth factors in PCa development and progression.

During ADT, increase in autocrine and paracrine growth factor loops results in deregulation of essential growth and survival pathways. EGF, TGF-α, IGF-1, keratinocyte growth factor (KGF) or basic fibroblast growth factor (bFGF) as well as their corresponding receptors are found to be overexpressed in CRPC [68–71]. IGF-1 is commonly overexpressed in the prostatic stroma and exerts mitogenic action on prostatic epithelial cells in a paracrine manner. High serum levels of IGF-1 is considered as a predictor for PCa and increased risk of malignancy [71,72]. In addition, bFGF such as FGF-2, FGF-7, and FGF-8 are overexpressed in both benign and malignant prostate cells and are indicative of uncontrolled proliferation, tumor metastasis, and exceedingly low survival rates [73,74]. TGF-β1 is often augmented in the serum of PCa patients and is related with bone metastasis and poor clinical outcome [75–77]. Numerous other studies have also recognized that changes in the levels of TGF-β and its pathway components contribute to PCa progression and cellular responses [78,79]. Overexpression of the EGF receptor (EGFR, ErbB-1) has also been documented during PCa and strongly correlates with biochemical relapse [80,81]. RTK Her-2/neu (ErbB-2) is also reported to be overexpressed in androgen-independently growing cell lines as well as in sublines that have been xenografted into castrated mice [82,83]. This in turn leads to activation of AR related genes through the Akt pathway resulting in enhanced metastatic and angiogenetic potential [84,85].

3.4. Phosphoinositide-3-kinase/AKT signaling

PI3K/AKT pathway, a chief intracellular signal transduction mechanism that links diverse classes of membrane receptors essentially plays a central role in cellular quiescence, cell growth, proliferation, differentiation, motility, survival and angiogenesis. In humans, PI3K

exists as a heterodimer of 110 kDa catalytic subunit and a 85 kDa regulatory subunit. Following stimulation by tyrosine kinase growth factor receptors such as EGFR; IGF-1R; G-protein-coupled receptors (GPCRs); cell adhesion molecules or oncogenic Ras, PI3K induces conscription and stimulation of the serine/threonine-specific protein kinase AKT via phosphorylation of the D3 position of phosphoinosities generating biologically active phosphatidylinositol (4,5) bisphosphate (PIP2) into phosphatidylinositol (3,4,5) trisphosphate (PIP3). PIP3 subsequently binds to AKT resulting in membrane translocation and its activation via phosphorylation. Activated AKT in turn phosphorylates and galvanizes several other proteins including mammalian target of rapamycin (mTOR) ultimately inducing and regulating a wide array of cellular processes [86]. Besides this, activation of mTOR by AKT can phosphorylate and inactivate 4E-BP1 (for eIF4E-Binding Proteins), a family of small acidic proteins that function as translational repressors of eIF4E. Phosphorylation of 4E-BP1 by mTOR releases 4E-BP1 from eIF4E thereby activating eIF4E involved translation-initiation complex and consequently the translational repertoire of a cell toward malignancy [87].

In 30%–50% of PCa patients, PI3K/AKT pathway is often augmented due to the loss of tumor suppressor PTEN (phosphatase and tensin homolog) that negatively regulates PI3K/AKT signaling by dephosphorylating PIP3 to PIP2 [86] [88]. In PCa cells, aberrant PI3K/AKT pathway disturbs the action of ERKs thereby favoring AR-independent growth. Congruently, AR target genes might impede PI3K/AKT pathway to favor AR-dependent growth in PCa cells [89,90]. Several mechanisms of cross-talk have been reported between AR and PI3K/AKT signaling. AKT can phosphorylate AR directly and inhibit activation of AR target genes, or PI3K/AKT signaling can regulate AR transcription via mechanisms other than AR phosphorylation [91,92]. Aberrations in PI3K pathway are also likely to constrain Ras/MEK/ERK pathway via amplified AKT activation. Besides, interrelationship between AKT and IGF signaling has also been reported in PCa cells. Upregulation of IGF, an upstream effector on AKT promotes PCa development *in vivo* [93,94]. Myc, a downstream PI3K/AKT target also interacts with AKT to endorse PCa development and progression. PI3K/AKT pathway can also act alongside with other proteins such as MST1, acetate Kinase (Ack1) and Bmi1 increasing their oncogenic potential [95,96]. PI3K/AKT is also known to increase the expression of MT1-MMP which are metalloproteinase receptors, thereby favoring PCa invasion and metastasis [90].

3.5. Janus Kinase/signal transducers and activators of transcription (JAK/STAT) signaling

JAK/STAT pathway is an imperative and pleiotropic membrane-to-nucleus cascade that transduces multitude of signals for normal development, cellular homeostasis, cell proliferation, differentiation, migration and apoptosis following stimulation by a wide variety of stimuli including reactive oxygen species, cytokines, and growth factors [97,98]. Briefly, activation of JAK/STAT pathway occurs when ligand binding induces multimerization of receptor subunits resulting in signal propagation via phosphorylation of receptor-associated JAK tyrosine kinases (JAK1, JAK2, JAK 3 and Tyk2). Principally, JAK activation occurs only upon receptor oligomerization as two JAKs are in close proximity ensuring *trans*-phosphorylation. Activated JAKs subsequently induce phosphorylation of other additional targets comprising both the receptors and STAT proteins. STATs reside in

the cytosol as dormant transcription factors and become activated following phosphorylation by JAKs at conserved C-terminal tyrosine residue. Phosphorylation in turn induces dimerization of STATs through conserved SH2 domain subsequently allowing their entry into the nucleus through importin α-5 and the Ran nuclear import pathway. In the nucleus, STATs bind to specific sequences in the DNA to stimulate or suppress transcription of target genes [99].

Inhibition of JAK/STAT3 signaling is reported to suppress PCa cell growth and induces apoptosis [100]. The DNA repair gene BRAC1 can induce cell proliferation and inhibit apoptotic cell death in PCa cells through interaction with JAK1/2 and STAT3 phosphorylation [101]. AR can also associate with STAT3 and activate JAK/STAT pathway to stimulate cell proliferation and antiapoptotic effects. In addition, activation of STAT3 in PCa cells also stimulates various other genes that are associated with cell cycle progression, anti-apoptosis, angiogenesis and tumor invasion [102–104]. Besides, JAK2 can activate STAT5a/b in PCa cells via phosphorylation on conserved tyrosine residues Y694Stat5a and Y699Stat5b. This results in STAT5a/b dimerization and ensuing nuclear translocation where the dimer binding to specific response elements of target genes promotes prostate cancer growth, tumor progression and distant metastases [104–107]. Components of JAK-STAT pathway specifically pJAK-1 and pSTAT-3 function as predictors of biochemical relapse and poor prognosis of PCa [100].

3.6. MAPK pathway

MAPKs are serine-threonine kinases comprising of three distinct groups specifically ERKs, Jun N-terminal kinases (JNKs), and p38 isoforms. MAPK signaling links extracellular signals to the machinery that controls fundamental cellular processes such as growth, proliferation, differentiation, migration, apoptosis and transformation. Each MAPK signaling axis comprises of a three-tier kinase module: a MAPK kinase kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK. MAP3Ks phosphorylate and activate MAP2Ks, which in turn phosphorylate and activate MAPKs [108–110]. MAPK pathways are activated either by a sequence of binary interactions between the kinase components or via formation of a signaling complex containing multiple kinases guided by a scaffold protein. While kinase suppressor of Ras-1 (KSR) and MEK partner 1 (MP1) function as scaffold proteins for the ERK pathway, JNK-interacting proteins (JIPs) serve as scaffold proteins for the JNK pathway. β-Arrestin 2 acts as a scaffold protein for both the ERK and JNK signaling pathway [111]. Upon activation, the MAPKs phosphorylate various substrate proteins including transcription factors such as c-Jun, c-Fos, ATF2, and p53. Erk or p38 MAPKs can also activate MAPK interacting protein kinases 1 and 2 (MNK1 and MNK2) that play important roles in controlling signals involved in mRNA translation [112]. Phosphorylation of MNKs 1 and MNK2) by MAPK activates its kinase activity as well as to enhances its binding to the eukaryotic initiation factor 4G (eIF4G) which functions as a scaffolding protein. Additionally MNK mediated phosphorylation of eIF4E regulates its release from eIF4G which along with its binding partners and the small ribosomal subunits constitute vital components of the 48S initiation complex required for cap-dependent translation initiation. Activation of the eIF4E by MNKs promote the translation of a subset of mRNAs are referred to as ‘eIF4E-sensitive’ most of which includes proliferation and survival-

promoting proteins such as cyclin D1 and D3, c-Myc, MDM2 (mouse double minute 2), VEGF, survivin and Bcl-2 (B-cell lymphoma 2) [113,114].

Overexpression of EGF, FGF, IGF, and KGFs in PCa frequently results in activation of endogenous Ras and MAPK pathways [115–117]. Overexpression of Ras and its mutant form also promotes castration resistance in LNCaP cells endorsing tumorigenicity [118]. p38 signaling chiefly activated at later stages of PCa increases the expression of aquaporins which are pore-forming proteins thereby enabling PCa cells survive through hypoxia [119,120]. Besides, MNKs and p-eIF4E are also found to be highly overexpressed in PCas [25–27] [25–27]. The Oncomine database documents that MNK2 is overexpressed 1.5 to 4.4-fold in hormone resistant and metastatic prostate tumors [121]. Increased MNK activity is documented to promote proliferation in PCa cells [25–27,122].

3.7. Wnt/β-catenin signaling

Wnt/*β*-catenin pathway is a highly conserved developmental signaling pathway comprising of secreted glycoproteins that play a vital role in tissue homeostasis, cell proliferation, differentiation, migration, and epithelial-mesenchymal communications, polarity and asymmetric cell division [123]. Based on the ability to stabilize the multifunction protein β-catenin, Wnt signaling is subdivided into canonical pathway and the noncanonical (planar cell polarity or Wnt/calcium) pathway. β-catenin predominantly exists in the cytosol in complex with adenomatous polyposis coli (APC), axin, casein kinase 1 (CK1), and glycogen synthase kinase 3β (GSK-3β). In the absence of Wnt signal, GSK-3β and CK1, phosphorylate β-catenin at specific serine/threonine residues leading to its ubiquitination and proteasomal degradation via F-box/WD repeat-containing protein 1A (FBXW1A)/S-phase kinase-associated protein (SKP) complex. In contrast, binding of Wnt ligands to frizzled receptors (FZD) hyperphosphorylates and activates disheveled proteins (DVL). Activated Dvl in its turn displaces GSK-3β from the β-catenin complex thereby averting GSK-3β-mediated phosphorylation and consequent degradation of β-catenin. As a result, free β-catenin accumulates in the perinuclear region forming a pool of free signaling molecules which ultimately interact with lymphoid enhancer factor/T cell factor (LEF/TCF) in the DNA to stimulate transcription of various target genes including that of c-Myc, p300, Foxo, Bcl9–2, c-Jun, CtBP, and cyclin D1 through displacement of groucho-HDAC co-repressors [124–128].

Increased expression of β-catenin occurs quite commonly in PCa due aberrant AKT signaling which results in phosphorylation and inactivation of GSK3β which favours formation of uncomplexed cytosolic β-catenin [129]. Besides, mutant forms of β-catenin have also been discovered in PCa. The mutant forms of β-catenin surpass normal mechanisms of phosphorylation by GSK3*b* and further degradation via the ubiquitin pathway [130,131]. During PCa, β-catenin is also found to associate with AR thereby enhancing expression of various growth and proliferative genes [132]. Expression of Wnt ligands is high in PCa and correlates with disease progression, higher Gleason scores, augmented PSA, and metastasis [133–135]. In addition to Wnts, frizzled receptors are also upregulated during PCa. Specifically, FZD4 overexpression is common in PCa and favours epithelial-to-mesenchymal transition [135,136].

4. Novel therapeutics targeting key signalling pathways in PCa

So far, Food and Drug Administration (FDA) has approved 19 agents for PCa therapy and treatment [137–158]. Fig. 2 represents the chemical structures of some of the drugs approved and in advanced development for PCa treatment. The majority of these agents are hormonal modulators targeting the androgen pathway. The gonadotropin-releasing agonists such as leuprolide (Lupron), goserelin (Zoladex), and triptorelin (Trelstar) that block the release of LHRH, and anti-androgens such as bicalutamide (Casodex), flutamide (Eulexin), and nilutamide (Nilandron) that help block the action of testosterone in PCa cells have been the backbone of PCa treatment [137–143]. However, for advanced PCa specifically CRPC limited treatment options exist providing avenues for the development of newer agents targeting AR and other major signaling cascades.

4.1. Inhibitors of AR signaling

In depth understanding of AR signaling and the mechanisms of castration resistance in PCa has resulted in the development of novel agents that can more efficiently retract AR signaling. Abiraterone acetate (Zytiga) is a selective, oral agent that can irreversibly inhibit the enzymatic activity of CYP17A1, a key member of the cytochrome p450 family with dual functions of 17a-hydroxylase and C17,20-lyase activity. It catalyzes the 17α-hydroxylation of steroid intermediates that is critical in testosterone biosynthesis. The blockade of CYP17A1 by Abiraterone thus decreases androgen synthesis in adrenal glands, testes, and tumor cells. Abiraterone has been shown to reduce serum testosterone levels to below a detection threshold of 1 ng/dL [159]. Abiraterone is 10- to 30-fold more potent CYP17 inhibitor than ketoconazole, a broad spectrum antifungal agent that has been extensively used as second-line hormonal therapy for PCa due to its ability to inhibit 11-β hydroxylation, cholesterol side chain cleavage to pregnenolone and CYP17 [160,161]. MDV3100 (Enzalutamide) is a potent oral antagonist. As opposed to firstgeneration anti-androgens, MDV3100 is an anti-androgen with multiple effects on AR- it is a competitive inhibitor of the C-terminus ligand-binding domain, besides it also prevents AR nuclear translocation, AR binding to DNA, and co-activator recruitment. MDV3100 exhibits a 5- to 8-fold greater activity than bicalutamide and only 2- to 3-fold reduced activity compared with the native ligand dihydrotestosterone [162–164]. While abiraterone and enzalutamide show survival benefit in castrate-resistant disease, PCa cells eventually develop resistance [165–167]. Galeterone (VN/124–1, TOK-001) developed by Tokai Pharmaceuticals is a 17-heteroazole steroidal analogue currently in pivotal phase 3 clinical trial for men with metastatic, castration-resistant PCa or CRPC, whose prostate tumor cells express the AR-V7 splice variant [168]. Galeterone disrupts the androgen receptor signaling by functioning in 3 ways: (i) androgen receptor degradation, which reduces the amount of androgen receptor in tumor cells (ii) CYP17 enzyme inhibition, which blocks the synthesis of testosterone (iii) androgen receptor inhibition, which blocks the binding of testosterone or DHT with the androgen receptor [169–171].

4.2. Inhibitors of growth factor signaling, RTK and PI3K/AKT/mTOR pathway

Several inhibitors of key intracellular signaling pathways that are aberrant in PCa such as IGF, RTK and PI3K/AKT/mTOR signaling are also being actively investigated either as

single agents or in combination for PCa treatment and therapy. Drugs targeting IGF-1R signaling are broadly classified as (A) neutralizing antibodies and (B) small molecule inhibitors of the IGF-1R tyrosine kinase activity (eg: BMS-754807, NVP-ADW742, NVP-AEW541, OSI-906, XL228). Besides blocking IGF-1R activity, the neutralizing antibodies (AMG-479, cixutumumab or IMC-A12, figitumumab or CP751,871, MK0646, R-1507, Sch-717454) also down-regulate IGF-1R overtime by promoting receptor internalization [172]. Inhibitors of PI3K/Akt pathway are also in clinical development. They are grouped into four main classes as PI3K inhibitors, Akt inhibitors, mTOR inhibitors and dual PI3K–mTOR inhibitors. The PI3K inhibitors are further divided into isoform-specific inhibitors or pan-PI3K inhibitors and include XL147, PX866, GDC0941, BKM120, and CAL101. Akt inhibitors comprise of ATP mimetics and non-catalytic site inhibitors. Examples of Akt inhibitors include perifosine, GSK690693, VQD002 and MK2206. Dual PI3K–mTOR inhibitors target the p110α, β and δ isoforms, mTORC1 and mTORC2 as the p110 subunits of PI3K and mTOR share similar structures. Examples of this class of inhibitors include BEZ235, BGT226, XL765, SF1126 and GSK1059615. mTOR inhibitors directly inhibit catalytic site of mTOR including mTORC1 and mTORC2. Examples of this kind include OSI027, AZD8055, CCI-779, and RAD-001 (Everolimus) [173–176].

Several small molecule inhibitors of Src family of kinases (SFKs), a group of non-receptor tyrosine kinases that play crucial role in PCa development, progression and metastasis have been developed and are under clinical testing. Of these, Dasatinib is the first FDA approved SFK/ABL dual inhibitor. Dasatinib in addition to inhibiting Fyn, Yes, Src, and Lyk- the Src family of kinases, also obstructs BCR-ABL, EphA2, platelet-derived growth factor receptor, c-Kit, MAPKs and RTKs resulting in suppression of cell adhesion, migration and invasion. Other SFK inhibitors under clinical testing include saracatinib (AZD0530) and bosutinib (SKI-606) [177–181]. A phase II trial of AZD0530 induced durable PSA responses in patients with advanced CRPC [182].

4.3. RANKL inhibitors

Preclinical studies in prostate cancer xenografts have firmly established that blockade of receptor activator of nuclear factor-κB (RANK) signal instigated by binding of RANK ligands (RANK-L) impairs the establishment and progression of bone metastasis [183]. Denosumab, a fully human monoclonal antibody is an FDA approved drug for treating metastasis in men with PCa. It binds specifically binds to and antagonizes RANK-L function thus alleviating bone reabsorption. Besides, Denosumab can also directly inhibit osteoclasts to abrogate bone reabsorption [183,184].

4.4. Taxanes and epothilones

Taxanes [Paclitaxel (Taxol) and Docetaxel (Taxotere)] encompass a class of cytotoxic chemotherapeutic agents that has been shown to provide a survival benefit in advanced PCa, inhibiting tumor development and decreasing prostate-specific antigen (PSA) levels. The mechanism of action of taxanes involves the stabilization of microtubules. Taxanes block cell cycle progression through centrosomal impairment, stimulation of abnormal spindle formation and destruction of spindle microtubule dynamics. Taxanes are also suggested to influence AR function by reducing the expression of AR-activated genes [185]. Tubulin

mutations and overexpression of ATP-dependent drug efflux pump P-glycoprotein are key factors chemoresistance to taxanes [186]. Efforts to overawe resistance to taxanes have resulted in the development of epothilones and cabazitaxel, which are novel tubulin-binding agents [187,188]. Epothilones are macrolide antibiotics which are structurally different from taxanes in their tubulin-binding site. They induce stabilization of microtubules via binding near the taxane-binding site resulting in cell death and tumor regression [187]. Ixabepilone, a semisynthetic derivative of the natural epothilone B is reported to be active against metastatic CRPC in chemo-naive and docetaxel-refractory CRPC [189]. Cabazitaxel (Jevtana) is a potent, second-generation, semisynthetic taxane. Although it functions as a microtubule inhibitor similar to docetaxel and paclitaxel and binds to tubulin, leading to microtubule stabilization, inhibition of mitosis and cell death, it exhibits poor affinity for P-glycoprotein-mediated efflux pumps. Hence cabazitaxel benefits patients with demonstrated taxane resistance. Besides it can also penetrate the blood brain barrier to a greater extent than docetaxel and paclitaxel, further augmenting its ability to target metastatic brain lesions [188]. Table 2 summarizes the mechanism of actions of some of the approved/ in development PCa drugs.

5. Conclusions and prospects

A search of clinicaltrials.gov for new PCa protocols registered during the past 3 years identified 783 protocols (search criteria: search term = PCa; study type = interventional; first received = from 01/01/2013 to 01/28/2016). Of these, drug interventional studies total to 452, of which 45 protocols were for CRPC [190]. Hence a great deal of effort has been made in the past few years to develop new therapeutic options for PCa, in particular CRPC. A constellation of “potential PCa targets” have been uncovered in recent years resulting in a large number of new agents specifically belonging to the innovative classes of targeted therapy. However, it is still not sure whether a multi-targeted approach that concurrently inhibits diverse signaling cascades including their feedback activation will result in a well-tolerated additive/synergistic therapeutic effect. Besides, another major challenge is the identification of appropriate biomarkers that will predict clinical response from targeted novel therapeutics in heterogeneous PCa patients. Hence, it is foremost to identify biomarkers that correlate well with overall survival and promising antitumor activity in conjunction with the development of targeted agents. Thus, with the development of effective targeted therapeutics that block key signaling cascades aberrant during PCa and its progression, and identification of biomarkers that accurately validates the efficacy of these therapeutics, we anticipate that survival and well-being in patients with PCa will improve significantly in the years ahead.

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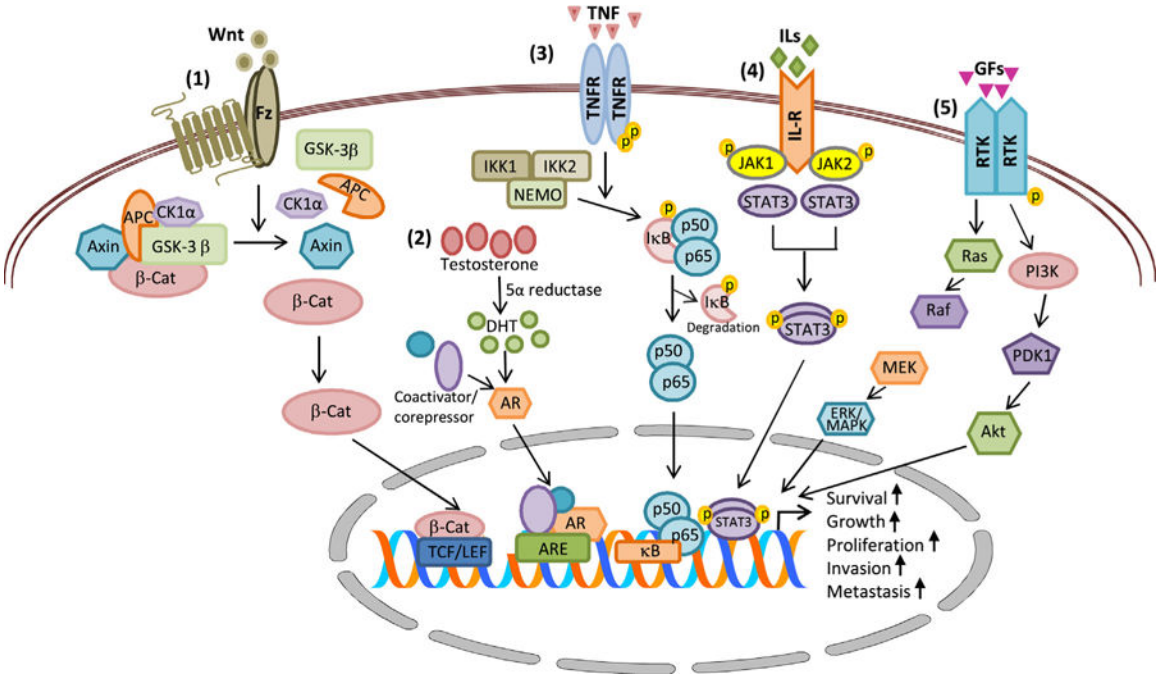

Fig. 1.

Chief signaling pathways involved in PCa development and progression. (1) Wnt/β-catenin signaling, (2) AR signaling, (3) NF-κB signaling, (4) JAK/STAT signaling and (5) receptor tyrosine kinase signaling. Abbreviations: AKT, akt serine/threonine kinase; AR, androgen receptor; ARE, androgen responsive elements; β-Cat, beta-catenin; DHT, dihydrotestosterone; GF, growth factor; Fz, Frizzled receptor; IκB, inhibitor of *kappa* B; ILs, interleukins; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide-3-kinase; Ras, rat sarcoma protein; RTK, receptor tyrosine kinase; STAT, signal transducers and activators of transcription; TCF/LEF-1, t-cell specific transcription factor/lymphoid enhancer-binding factor; Wnt, wnt ligands.

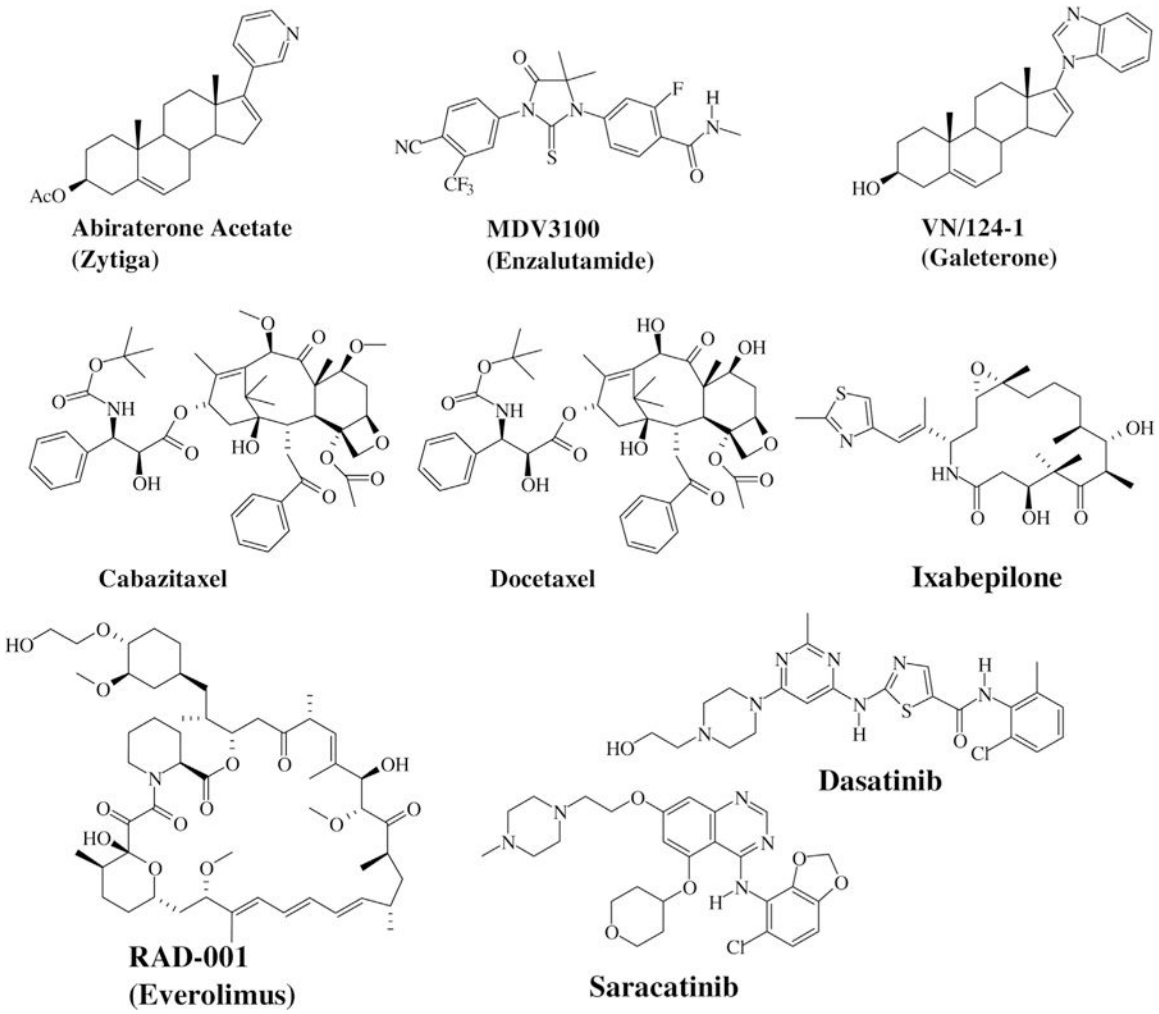

Fig. 2.
Chemical Structures of some of the approved/in development Prostate Cancer Drugs.

Table 1

Role of growth factors in prostate cancer development and progress.

Growth Factor	Role in prostate cancer
Adrenomedullin	*Role in hormone-independent tumor growth and angiogenesis*
Angiopoietin	*Regulator of angiogenesis*
Autocrine Motility Factor (AMF)	*Cell motility and metastatic dissemination*
Bone Morphogenetic Protein (BMPs)	*Bone metastasis*
Brain Derived Neurotrophic Factor (BDNF)	*Apoptosis evasion*
Epidermal Growth Factor (EGF)	*Promotes cell migration, adhesion, and proliferation*
Erythropoietin	*Growth regulation*
Fibroblast Growth Factor (FGF)	*Bone metastasis*
Growth Differentiation Factor (GDF)	*Promotes cell adhesion and motility*
Hepatocyte Growth Factor (HDGF)	*Promote cell invasion and epithelial to mesenchymal transition*
Insulin-like Growth Factors (IGFs)	*Vital roles in cell proliferation, apoptosis evasion and invasion*
Nerve Growth Factors (NGF) and other neurotrophins	*Cancer cell proliferation and apoptosis evasion*
Platelet-Derived Growth Factors (PDGF)	*Promoter of tumor angiogenesis and bone metastasis*
Transforming Growth Factor-β (TGF-β)	*Promotes extracellular matrix production, induces angiogenesis, and inhibits host immune function*
Tumour Necrosis Factor-α (TNF-α)	*Inflammatory processes in tumor promotion*
Vascular Endothelial Growth Factor (VEGF)	*Plays a positive role in promoting angiogenesis*
Placental Growth Factor (PlGF)	*Promotes neovascularization*

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Table 2

Mechanism of action of some of the approved/in development PCa drugs.

S.No.	Name/Trade name	Mechanism of action/target
1.	Abiraterone actate (Zytiga)	CYP17 inhibitor
2.	MDV3100 (Enzalutamide)	Androgen-receptor (AR) antagonist
3.	VN/124-1 (Galaterone)	Androgen receptor antagonist, AR degradation, CYP17 inhibition
4.	Cabazitaxel	Microtubule inhibitor
5.	Docetaxel	Microtubule inhibitor
6.	Ixabepilone	Antimicrotubular agent
7.	RAD-001 (Everolimus)	mTOR inhibitor
8.	Dasatinib	Tyrosine kinase inhibitor
9.	Saracatinib	Dual kinase inhibitor (Src and Bcr-Abl tyrosine-kinase inhibitor)
10.	Denosumab	RANKL inhibitor

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