




Review

The Molecular Biology of Prostate Cancer Stem Cells: From the Past to the Future

Yong Zhou [†], Tian Li [†], Man Jia, Rongyang Dai ^{*} and Ronghao Wang ^{*†} 

Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Southwest Medical University, Luzhou 646000, China

^{*} Correspondence: dryrun2502@swmu.edu.cn (R.D.); ronghao_wang@swmu.edu.cn (R.W.); Tel.: +86-18989132798 (R.D.); +86-18483057856 (R.W.)

[†] These authors contributed equally to this work.

Abstract: Prostate cancer (PCa) continues to rank as the second leading cause of cancer-related mortality in western countries, despite the golden treatment using androgen deprivation therapy (ADT) or anti-androgen therapy. With decades of research, scientists have gradually realized that the existence of prostate cancer stem cells (PCSCs) successfully explains tumor recurrence, metastasis and therapeutic failure of PCa. Theoretically, eradication of this small population may improve the efficacy of current therapeutic approaches and prolong PCa survival. However, several characteristics of PCSCs make their diminishment extremely challenging: inherent resistance to anti-androgen and chemotherapy treatment, over-activation of the survival pathway, adaptation to tumor micro-environments, escape from immune attack and being easier to metastasize. For this end, a better understanding of PCSC biology at the molecular level will definitely inspire us to develop PCSC targeted approaches. In this review, we comprehensively summarize signaling pathways responsible for homeostatic regulation of PCSCs and discuss how to eliminate these fractional cells in clinical practice. Overall, this study deeply pinpoints PCSC biology at the molecular level and provides us some research perspectives.

Keywords: PCa; cancer stem cells; signaling pathway



Citation: Zhou, Y.; Li, T.; Jia, M.; Dai, R.; Wang, R. The Molecular Biology of Prostate Cancer Stem Cells: From the Past to the Future. *Int. J. Mol. Sci.* **2023**, *24*, 7482. <https://doi.org/10.3390/ijms24087482>

Academic Editor: Niall M. Corcoran

Received: 20 March 2023

Revised: 3 April 2023

Accepted: 11 April 2023

Published: 19 April 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Prostate cancer (PCa) is the most common urological malignancy and brings great health threats to men. A recent global survey indicated that approximately 1.4 million new cases of and 375,000 deaths from PCa were documented in 2020 [1], which will display an increasing trend as PCa is an age-related disease. Prostate gland epithelial cells are mainly composed of two primary types of cells [2,3]: basal cells and luminal cells. Luminal epithelial cells are those well-differentiated androgen-dependent cells characterized by the high expression of androgen receptors (AR) and cytokeratins (CKs) [4–6], while basal epithelial cells tend to express a cluster of differentiation molecule 44 (CD44), keratin 5 (KRT5) and tumor protein 63 (P63) [4,7–10]. PCa shares biological similarity with luminal epithelial cells and is primarily driven by AR signaling [4,11,12]. PCa is dormant, and newly diagnosed cases only need active surveillance by periodically performed prostate specific antigen (PSA) testing, digital rectal examination (DRE) and biopsy [13,14].

It is worth noting that the 5 year survival rate of localized PCa is closed to 100%. However, PCa with bone or lymph node metastasis only has an approximately 30% 5 year survival rate, which is the main cause of PCa-related death [15]. Thanks to the pioneer study by Charles Huggins et al., androgen deprivation therapy (ADT) has been utilized as the golden management of advanced PCa [16]. Unfortunately, the duration of ADT only lasts 2–3 years and castration-resistant prostate cancer (CRPC) eventually develops [17,18]. At this stage, AR signaling is reactivated via several mechanisms and nicely responds to the castrated androgen level, supporting CRPC survival [19–22]. To further block AR

signaling, the more powerful anti-androgen enzalutamide and adrenal androgen synthesis inhibitor abiraterone have been approved by the FDA to treat metastatic CRPC [23–26], with promising survival benefit. However, both of them only prolong CRPC patients' survival for about 5 months.

There is a small population of prostate cancer cells existing in PCa, called prostate cancer stem cells (PCSCs), prostate progenitor cells or prostate initiating cells, contributing to PCa development [27]. Mounting evidence suggests that they play overarching roles in PCa initiation, progression and AR targeted therapy resistance [28,29], suggesting that eradication of this tiny population may be a promising strategy to fight against PCa. However, it is a big challenge to diminish such populations because they are inherently resistant to current treatments and extremely adaptive to the tumor's micro-environment. Moreover, PCSCs evolve to activate survival signaling but suppress apoptosis signaling. For this end, a deep understanding of the molecular biology of PCSCs may give us some insights on how to eliminate these cells. This review will summarize the signaling pathways to this date related to the biology of PCSCs and discuss their potentially clinical applications.

2. Prostate Cancer Stem Cell

Cancer cell heterogeneity can result from the differentiation program driven by a subset of unique cancer cells called cancer stem cells (CSCs), which have self-renewal potential and can differentiate into various types of cells in a symmetrical or asymmetrical cell divided manner [30–32]. In 2005, with the successful isolation of CD44+/ α 2 β 1^{hi}/CD133+ enriched cells from a human prostate tumor, Collins et al. found that this small population of PCa cells possessed self-renewal ability and were enabled to differentiate into non-clonal tumor cells [33]. Other studies also demonstrated that CD44+ and PSA^{-/lo} PCa cells shared similar properties with CD44+/ α 2 β 1^{hi}/CD133+ enriched cells [34–36]. With decades of research, scientists have gradually recognized the existence and significance of these fractional cells in PCa using various biomarkers (Table 1) [37–61], which have stem cell characteristics and are then referred as PCSCs. Now, it is clear that PCSCs are involved in the initiation, progression and therapeutic resistance of PCa.

Table 1. Biomarkers for prostate cancer stem cells.

Marker	Function	Reference
CD44	CD44 is a glycoprotein involved in cell migration, adhesion and signal transduction	Kalantari E, et al., 2017 [37]
CD133	CD133 is a transmembrane glycoprotein involved in cell self-renewal, differentiation and tumor invasion	Kalantari E, et al., 2017 [37]
CD117	CD117 is a transmembrane glycoprotein involved in cell self-renewal, differentiation and tumor invasion	Harris KS, et al., 2021 [38]
α 2 β 1	α 2 β 1 is associated with tumor invasion and proliferation	Aldahish A, et al., 2019 [39] Naci D, et al., 2015 [40]
EpCAM	EpCAM is a calcium independent adhesion molecule between epithelial cells involved in the process of epithelial cell carcinogenesis	Witte KE, et al., 2021 [41]
SOX2	SOX2 plays an important role in maintaining stem cell pluripotency and self-renewal	Lee Y, et al., 2021 [42] Vaddi PK, et al., 2019 [43]
EZH2	EZH2 is closely related to cell migration and invasion, tumor development and stem cell self-renewal	Huang J, et al., 2021 [44]
CXCR4	CXCR4 is a specific receptor involved in physiological mechanisms such as HIV-1, hematopoiesis, embryonic development and tumor migration	Li Y, et al., 2019 [45] Chatterjee S, et al., 2014 [46]
TRA-1-60	A cell surface epitope of human embryonic, embryonal germline and teratocarcinoma stem cells	Schafer C, et al., 2020 [47]
CD151	CD151 is associated with tumor initiation, metastasis, and angiogenesis	Wong AH, et al., 2020 [48]

Table 1. Cont.

Marker	Function	Reference
Smo	Smo is a transmembrane protein that mediates Hedgehog signaling to the intracellular compartment	Lou H, et al., 2020 [51]
Nanog	Nanog is a transcription factor with an important role in stem cell self-renewal and maintenance of pluripotency	Verma S, et al., 2020 [52] Liu C, et al., 2020 [53]
Bmi-1	Bmi-1 is associated with maintenance of self-renewal of prostate stem cells and inhibition of PTEN in PCa	Li Y, et al., 2017 [54] Yoo YA, et al., 2016 [55]
TWIST	TWIST is a transcription factor with a helix-loop-helix structure and associated with tumor invasion and metastasis	Lee Y, et al., 2021 [42]
CD24	CD24 is a cell adhesion molecule involved in the regulation of B-cell proliferation and maturation	Costa CD, et al., 2019 [56]
CD166	CD166 is a leukocyte adhesion factor associated with cell adhesion and tumor metastasis	Wei GJ, et al., 2019 [57] van Lersner A, et al., 2019 [58]
CD49b	CD49b is also called integrin $\alpha 2$, a cell surface receptor associated with adhesion and lymphocyte activation	Bansal N, et al., 2016 [59] Erb HHH, et al., 2018 [60]
ABCG-2	ABCG-2 contributes to the resistance to chemotherapeutic drugs	Kim WT, et al., 2017 [61]

2.1. The Role of PCSCs in PCa Initiation

A number of literature studies have highlighted cancer stem cells as the origin of tumor initiation, including PCa. In the prostate gland, a small population of prostate stem cells (PSCs) undergo an oncogenic transformation to PCSCs when the external environment is unfavorable (Figure 1). Then, the omnipotent PCSCs give rise to various sub-types of prostate cancer cells, either AR-dependent or -independent, forming PCa heterogeneity. It seems that luminal-like PCa originates from progenitor cells in luminal epithelial cells. However, $\alpha 2\beta 1^{\text{hi}}/\text{CD}133^+$ prostate stem cells were previously identified to be located in the basal layer [62]. Moreover, Witte et al. impressively found that it was the basal epithelial cells, but not luminal epithelial cells, growing to the prostate gland structure when they were subcutaneously implanted into nonobese diabetic scid gamma (NSG) mice [63]. Another study revealed that only basal epithelial cells with oncogenic induction led to prostatic intraepithelial neoplasia (PIN) and PCa in NSG mice [64]. All these findings together suggest that PCSCs in basal epithelial cells are the origin of PCa.

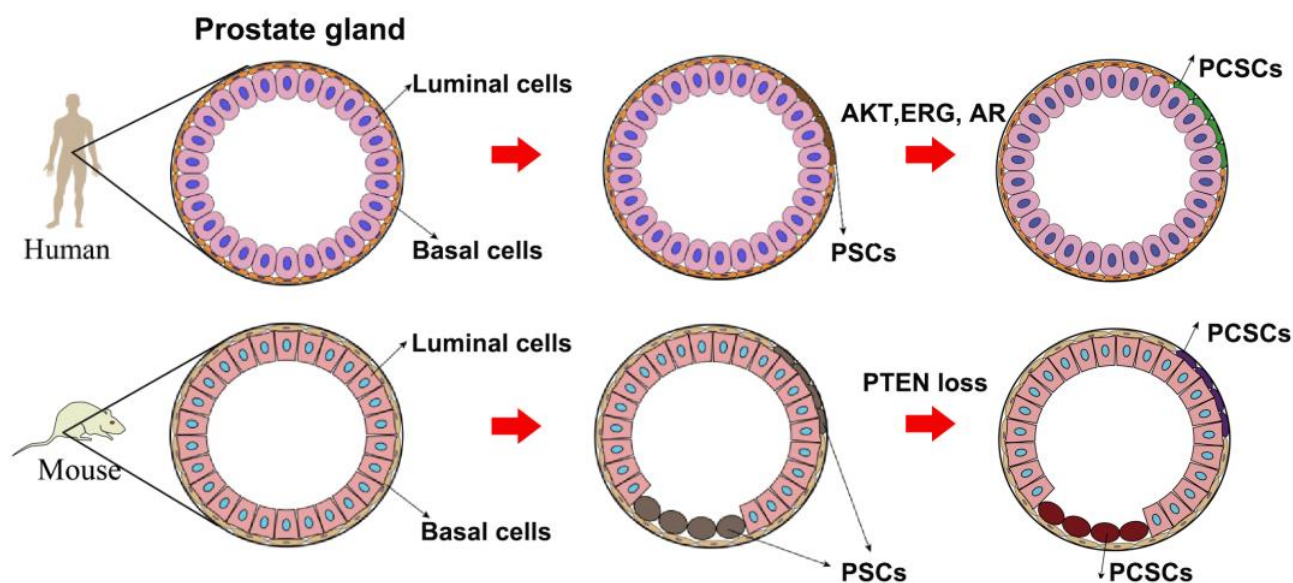


Figure 1. A model of the origin of prostate cancer stem cells.

However, the origin of PCa in mice is different from that in humans. Studies by lineage tracing system elucidated that PSCs can be found in both the luminal and basal layers [65,66]. Further investigation illuminated that phosphatase and tensin homolog (PTEN) loss in either the basal layer or luminal layer led to PCa development. In the view of a CSCs-based hypothesis, PSCs in either the luminal layer or basal layer will transform to PCSCs when suffering from genetic alteration such as PTEN loss [67]. Although there is a little discrepancy between mouse PCa and human PCa regarding their origin (Figure 1), the concept of PCSCs as PCa origin has been widely acknowledged by many scientists: PSCs in the prostate epithelial cells undergo genomic instability to give rise to PCSCs when the environment is unfavorable, finally leading to PCa development.

2.2. The Role of PCSCs in PCa Progression and Anti-Androgen Resistance

PCa with 2–3 years ADT treatment will eventually develop to castration-resistant disease, a lethal stage owing to its metastatic potential. By bypassing this systemic androgen suppression, AR signaling hijacks several means in order to efficiently respond to the castrated androgen level. AR amplification, AR mutation and selective up-regulation of AR co-regulators are the more frequently observed biological processes in CRPC as compared with primary tumors [12,68–70].

Growing evidence also illustrates that ADT treatment expands the population of PCSCs [29,71,72], which have no response to androgenic sources. Continuous AR signaling inhibition of CRPC is fulfilled by the treatment of FDA approved anti-androgen enzalutamide [23,26], which competes androgen to bind AR and suppresses AR nuclear imports [73]. However, it only benefits CRPC by extending to a five month survival [74]. One popular mechanism responsible for the acquired enzalutamide resistance is the selective expression of truncated AR variants. For example, ARv7, which lacks an androgen responsive domain, is a crucially causal factor controlling enzalutamide resistance [75–77]. Another important mechanism responsible for anti-androgen resistance is lineage plasticity [78], which is possibly driven by PCSCs. Accumulative evidence suggests that AR-targeted therapies including ADT and anti-androgen treatment considerably enrich the population of PCSCs by facilitating the transition of AR-dependent PCa cells to AR-independent cells with stem-cell-like states or multi-lineage stages [79,80]. PCSCs then re-differentiate into AR-therapy-resistant sub-clones such as neuroendocrine PCa cells or other lineage sub-clones inherently resistant to enzalutamide treatment. In this regard, PCSCs play critical roles in PCa progression and anti-androgen resistance.

3. Signaling Pathways Maintain Prostate Cancer Stem Cell Population

As PCSCs play critical roles in PCa development and they are currently undruggable, understanding their biology is the priority if we want to minimize this small population. Therefore, we turn our focus to the signaling pathways that are causally linked to the survival and expansion of the PCSC population (Figure 2). In our opinion, this review of PCSC biology at the molecular level would interest a wide range of readers and inspire them to develop PCSC targeted therapy.

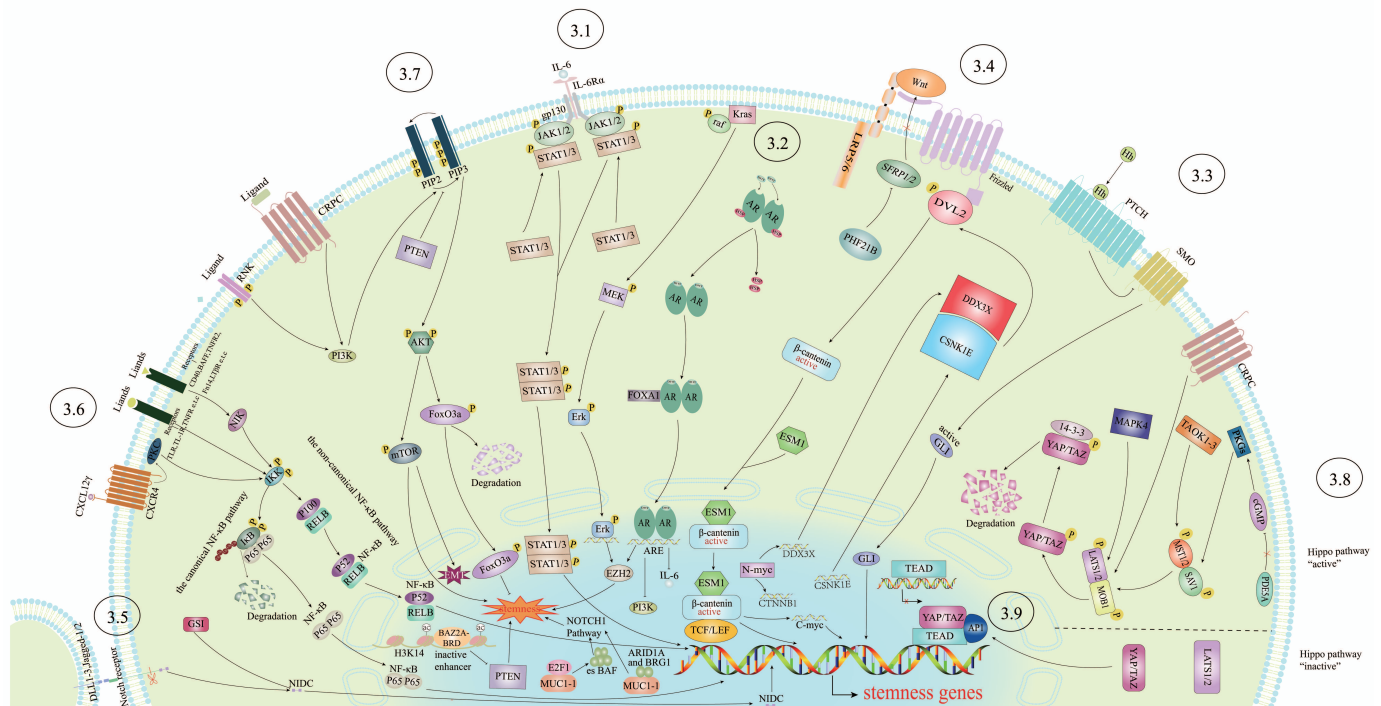


Figure 2. A schematic depiction of signaling pathways involved in PCSC biology.

3.1. Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) Signaling Pathway in PCSCs

The JAK-STAT pathway is implicated into various processes such as cell proliferation, anti-apoptosis and immune response [81,82]. The direct interaction of ligands (cytokines and interleukins) with the cell surface receptor leads to the trans-phosphorylation of JAK, which is recognized by the STAT protein. Subsequently, JAK phosphorylates the specific tyrosine residue of STAT and leads to its activation. Phosphorylated STAT dissociates from JAK and enters the nucleus as dimer to output its transcriptional activity [83,84].

STAT3, a member of the STAT family, has been illustrated as one of the fundamental driving forces to control the occurrence and development of various tumors [85–88]. In particular, STAT3 signaling is prone to be activated in CSC sub-populations. The maintenance of CSCs by STAT3 is probably attributable to its transcriptional regulation on CD44, CD133 and epithelial–mesenchymal transition (EMT) related genes [89,90]. Reciprocally, nuclear CD44 can complex with STAT3 and enhance its transcriptional activity [91,92]. In PCa, gene expression signature analysis identified that JAK1-STAT3 signaling was highly enriched in the CD133+/α2β1 integrin^{high} stem-like PCa sub-population [93]. It also demonstrated that STAT3 activation was a prerequisite for the survival of this type of PCSC [94]. Interestingly, the study also showed that ADT-driven AR inhibition could increase interleukin 6 (IL-6) levels, which triggers STAT3 activation by binding to glycoprotein 130 (gp130) receptors and leads to the subsequent expansion of the PCSC population, further supporting the critical role of STAT3 signaling in PCSC evolution [90,95]. In addition to IL6/gp130, STAT3 activation can be fulfilled by other factors. The literature reveals that monoamine oxidative A (MAOA), HOX transcript antisense RNA (HOTAIR), interleukin 10 (IL-10) and bacterial lipopolysaccharide (LPS) enable an increase in PCSC population via driving STAT3 signaling [96–98].

Now, new evidence illustrates that STAT1 can cooperate with STAT3 to promote the transition of AR-dependent PCa to stem-like cells with multilineage potential in an enzalutamide treated PCa model [28]. In this model, the authors found that SOX2 physically binds to the promoter region of *JAK1*, *STAT1* gene locus and increases their expression. Activated JAK1-STAT1 signaling regulates the expression of critical genes indispensable for lineage plasticity transition, conferring anti-androgen resistance. Indeed, genetic and phar-

maceutical inactivation of JAK1 can reverse the acquisition of lineage plasticity mediated enzalutamide resistance of PCa cells and human derived organoids.

Together, both STAT1 and STAT3 are central players during the process of anti-androgen-induced PCSC evolution, suggesting that combined therapy using their specific inhibitors would be a promising strategy to diminish PCSC populations and to overcome anti-androgen resistance.

3.2. AR Signaling in PCSCs

As one member of nuclear receptor, AR and NR3C4 have been widely acknowledged as the driving factor determining PCa initiation and progression. Once responding to androgenic hormones, AR imports to the nucleus and serves as a homo-dimer or hetero-dimer to regulate the expression of a variety of genes, supporting PCa survival [99]. The significance of AR in PCa development leads ADT and anti-androgen as the standardized therapies against this type of disease. However, studies have revealed that ADT and anti-androgen treatment result in the back-differentiation of some AR-positive PCa cells into PCSCs, which are inherently resistant to AR targeted therapies due to their negative AR characteristics. In a murine PCa model, the inhibition of AR with flutamide-activated IL-6/STAT3 signaling awakened PCSC growth, consistent with the aforementioned demonstration of IL-6/STAT3 signaling for the maintenance of PCSCs population [90]. Indeed, combined therapy of the IL-6 receptor fusion protein IL-6^{RFP} and flutamide could synergistically suppress murine PCa growth by blocking ADT-induced PCSC expansion. Accordingly, another literature study also suggested that NANOG, a critical stemness associated transcription factor, reprograms LNcaP cells to castration resistance via occupying the chromatin binding sites of AR [100]. Collectively, these data illuminate that AR signaling exerts an inhibitory effect on PCSC expansion. Contradictory to this notion, the results from Cai et al.'s study demonstrated that synergistic activation of Kirsten rat sarcoma virus G12D (Kras G12D) and AR in murine prostate cells resulted in aggressive PCa by expanding the PCSC population [101]. According to their data, Kras cooperates with AR to increase the expression level of the enhancer of zeste homolog 2 (Ezh2), which acts as one component of the polycomb repressive complex 2 (PRC2) complex to suppress the expression of differentiation-associated genes. For us, although AR/Kras derived PCa tumors have high levels of Ezh2, AR status in Ezh2-enriched PCSCs at the single cell level is still questionable. Overall, growing evidence suggests that PCSCs rarely express AR and AR, at least alone, suppresses PCSC survival.

3.3. Hedgehog (Hh) Signaling Pathway in PCSCs

Hedgehog signaling pathway activated by Hh ligands, including Sonic Hh (SHh), Indian Hh (IHh) and Desert Hh (DHH), is implicated into all aspects of cancer evolution [102]. The binding of Hh ligands to the twelve-pass trans-membrane protein receptor Patched1 (PTCH1) relieves the inactive Smoothed (SMO), a G protein-coupled receptor [103,104]. The active SMO, together with β -Arrestin (Arrb2) and kinesin family member 3A (Kif3a), promotes the trans-activation of full length glioma-associated oncogene homolog 1-3 (GLI1-3), regulating Hh targeting genes involved in the regulation of multiple aspects of tumorigenesis, including CSC homeostasis [105–107]. Indeed, literature by Han-Hsin Chang et al. demonstrated that aberrant activation of Hh signaling led to the transformation of normal prostate basal/stem cells into PCSCs, which further differentiated into metastatic cancer cells [108]. Results from another report revealed that intraprostatic delivery of Hh ligand to mice resulted in the development of aggressive prostate cancer [109]. Interestingly, the active Hh ligand was localized to the area of p63 positive cells, implying that Hh-induced PCa aggressiveness is attributable to the enrichment of PCSCs. In addition, genistein suppresses the tumorsphere formation of prostate cancer cells by acting as an Hh signaling inhibitor [110]. Together, all this evidence strongly reinforces the significant role of the Hh signaling pathway in PCSC evolution.

3.4. Wnt Signaling Pathway in PCSCs

Mounting evidence supports that the Wnt signaling pathway is indispensable for CSC homeostasis [111,112]. In PCa, the binding of the Wnt ligand with its receptor Frizzled and lipoprotein receptor-related protein (LRP)5/6 results in the stabilization and nuclear translocation of β -catenin, which acts as a cofactor of the T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factor family to regulate PCSC-related genes such as CD44 [113]. The literature demonstrates that β -catenin and its downstream targeting genes, such as axis inhibition protein 2 (Axin 2) and cyclin D, were highly enriched in human telomerase reverse transcriptase (hTERT) mediated PCSC traits [114]. Down-regulation of β -catenin by siRNAs remarkably attenuated hTERT mediated CSC features of prostate cancer cells. The critical role of Wnt signaling in maintaining the biology of PCSCs has also been strengthened by several literature studies, suggesting that the activation of Wnt signaling by PHD finger protein 21B (PHF21B), endothelial cell-specific molecule 1 (ESM1) or anaplastic lymphoma kinase (ALK) promotes PCSC phenotype [115–117]. The negative correlation of AR with β -catenin in primary PCa is shifted to the positive correlation in CRPC, implying that Wnt induced PCSC populations may contribute to castration resistance [118]. Indeed, the overexpression of active β -catenin results in resistance to castration, and the inhibition of Wnt signaling could overcome this phenomenon by reducing PCSC populations. Interestingly, a recent Science article demonstrated that PCa can be classified into four sub-types according to the molecular signature: AR-dependent PCa, cancer stem-like PCa, neuroendocrine PCa and Wnt-dependent PCa, highlighting the heterogeneous role of Wnt signaling in driving PCa progression, in addition to its definite role in the regulation of PCSC biology [119]. Indeed, β -catenin has been documented to activate AR signaling by forming a complex with AR. In conclusion, the Wnt signaling pathway is essential for the stemness of prostate cancer cells, even though its precise role in PCa development requires deep investigation.

3.5. Notch Signaling Pathway

Notch is a genetically conservative signaling transduction pathway implicated into various biological processes [120,121]. Interactions of Notch receptors (Notch1-4) with the specific ligands (Delta-like 1, Delta-like 3, Delta-like 4, Jagged-1 and Jagged-2) between adjacent cells triggers the proteolytic cleavage of the receptor and results in the release of the Notch intracellular domain (NICD), which trans-locates into the nucleus and guides a transcriptional switch of the CSL [CBF1/Su(H)/Lag-1] complex by releasing corepressors and recruiting coactivators. Cytoplasm-retained NICD is also functional via cross-talks with other signaling pathways such as protein kinase B (AKT), mammalian target of rapamycin complex 2 (mTORC2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B). Now, it is clear that abnormal activation of Notch signaling observed in PCa is causally linked to its initiation, angiogenesis, metastasis, drug resistance and CSC enrichment [122–124]. *Numb*^{-/low} CRPC sub-population with stem-like cell property prefers to express Notch targeting genes as compared with *Num*^{high} counterparts [125]. A recent study has shown that bone marrow mesenchymal stem cells (BMSCs) promote the stemness of prostate cancer cells via activating the Jagged1/Notch1 pathway [126]. Recently, Kufe et al. illustrated that MUC1-C can drive the expression of several BRG1/Brahma-associated factor (BAF) complex components in an E2F1-dependent manner. As feedback, BAF forms a nuclear complex with MUC-C1 to induce Notch1 expression and to promote the stemness of PCa [127]. Collectively, these data suggest that Notch signaling is a key player to determine PCa stem-like traits.

Given the fact that PCSC population enrichment is always considered as one critical resistant mechanism to anti-androgen or docetaxel treatment in PCa, targeting Notch signaling to eliminate PCSCs may increase the anti-androgen/docetaxel efficacy. Indeed, PF-03084014, a γ -secretase inhibitor (GSI) that prevents the cleavage of Notch receptors, can reduce the stemness characteristics of docetaxel-resistant or enzalutamide-resistant CRPC

cells and restore drug sensitivity [128,129]. Taken together, Notch signaling is over-activated in PCSCs and its inhibition is one potential strategy to minimize PCSC populations.

3.6. *NF- κ B Signaling Pathway in PCSCs*

The nuclear transcription factor NF- κ B family has five members (p65, RELB, c-REL, p50 and p52) and has been documented to control cancer cell survival, metastasis and CSC homeostasis [106,130,131]. Canonical NF- κ B signaling is initiated by the activation of the I κ B kinase (IKK) complex, which leads to the phosphorylation and subsequent degradation of I κ B. Without the mask of I κ B, NF- κ B members are released and translocated from the cytoplasm to the nucleus as either homo-dimers or hetero-dimers, enabling the transcription of targeted genes via specifically binding to its responsive DNA element [132,133]. In addition, NF- κ B signaling can be non-canonically activated in the form of p52/RELB dimer by other receptors such as B-cell activation factor (BAFFR), CD40, receptor activator for nuclear factor kappa B (RANK) and lymphotoxin b-receptor (LTbR) [134,135].

The role of NF- κ B in the homeostatic regulation of PCSCs was recognized by Rajasekhar et al., illustrating that isolated human tumor-initiating cells (TICs) with stem-cell-like properties exhibited active NF- κ B activity [136]. Significantly, the attenuation of NF- κ B signaling by its specific inhibitors, such as 481,407 compound, parthenolide and celastrol, suppressed the secondary sphere formation of TICs, supporting that NF- κ B activation is a prerequisite for PCSC expansion. In line with this finding, C-X-C motif chemokine ligand 12 (CXCL12) gamma, with its receptor C-X-C motif chemokine receptor 4 (CXCR4), enhanced PCSC phenotype by activating NF- κ B signaling [137]. Now, it is clear that the stemness related to NF- κ B signaling is at least partially attributable to its direct regulation on SOX9, one critical factor consistently increased in stem-like prostate cancer cells [138]. In the future, exploration of NF- κ B downstream effectors in regard to the regulation of PCSC homeostasis deserves scientists' considerable efforts.

3.7. *Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) Signaling Pathway in PCSCs*

PI3K/AKT is a highly conserved signaling pathway, and its disordered regulation is frequently observed in cancer development [139,140]. Usually, ligand bound membrane receptors such as G protein-coupled receptors (GPCR) or tyrosine kinase receptor (RTK) mediated PI3K activation results in the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3), which binds to AKT at the plasma membrane and leads to AKT phosphorylation by phosphoinositide-dependent kinase 1 (PDK1). Phosphorylated AKT is activated and exerts its biological functions via regulating a variety of downstream molecules such as tuberous sclerosis protein 2 (TSC2), forkhead box transcription factors of the class O (FOXO) and glycogen synthase kinase 3b (GSK3b) [141–144].

Aberrant activation of PI3K/AKT signaling by PTEN loss is frequently observed in 30% primary PCa and 60% CRPC [145]. The contribution of this signaling to PCSC expansion was recognized as early as 2009, when a literature study demonstrated that prostate cancer progenitors (PCaPs) cultured in sphere-forming conditions preferred to activate PI3K/AKT signaling by overexpressing PI3K p110a/b protein levels [146]. Mechanistically, the enrichment of the PCSC population was at least partially due to AKT-mediated nuclear export and degradation of FOXO3a, one critical transcription factor regulating the stemness of CSCs. Additional evidence suggested that the inhibition of PI3K/AKT signaling by LY294002 and NVP-BEZ235 indeed noticeably suppressed the survival and sphere forming ability of PCa cells [147,148]. In agreement with this finding, L Chang and his colleagues also elucidated that the PI3K/AKT regulated stemness phenotype was causally associated with the radio-resistance of PCa [149]. The significant and complex role of PI3K/AKT signaling in PCa prompted clinical trials of its inhibitors as a therapeutic strategy for metastatic CRPC, although they finally failed.

New evidence suggests that the strong inhibition of AR by the second anti-androgen selects activating PI3K/AKT signaling to develop anti-androgen resistant CRPC [150]. We

thus believe combined therapy targeting AR and PI3K/AKT signaling is a fascinating strategy to treat metastatic CRPC, and is indeed intensively tested in clinical trials.

3.8. Hippo Signaling Pathway

The Hippo signaling pathway acts as a crucial regulator during cell growth and organ development and is controlled by a kinase cascade [151,152]. In the active status, a mammalian STE20-like protein kinase 1/2 (MST1/2), G protein coupled receptor (GPCR), or mitogen-activated protein kinase kinase kinase (MAP4K) family member acts as the upstream molecule to phosphorylate tumor suppressor kinase LATS1/2 (large tumor suppressor kinase 1/2), which subsequently phosphorylates Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), leading to their cytoplasmic retention and degradation [153]. When Hippo signaling is silent, YAP/TAZ is dephosphorylated and translocated into the nucleus, initiating gene transcription via binding to the TEAD family of transcription factors [154–156].

Activation of YAP/TAZ caused by either mutation on Hippo pathway upstream molecules or the cellular regulatory network promotes tumorigenesis and cancer stem-like phenotype [157,158]. The role of the Hippo pathway in PCSC biology has been recognized by this study, which demonstrated that the inhibition of phosphodiesterase 5 (PDE5) by its specific inhibitor vardenafil attenuated PCSC phenotype by activating cGMP-dependent protein kinases (PKGs), which triggered the Hippo signaling cascade by directly phosphorylating MST1/2, thereby degrading TAZ to achieve the purpose of downregulating the stemness of PCSCs [159]. In addition, CD44, a popular biomarker of PCSCs, promoted the invasion and metastasis of docetaxel-resistant PCa cells by inducing the expression of YAP [160]. Together, the Hippo inactivation mediated nuclear accumulation of YAP/TAZ accentuated PCSC phenotype and configuration of YAP/TAZ transcriptional complex or the upstream regulators may become the research direction in this field.

3.9. The Activator Protein-1 (AP1) Transcription Factor

AP-1 protein is a transcription factor with a basic leucine zipper domain and acts as a homo-dimer or hetero-dimer to regulate gene expression, participating in various cellular processes including proliferation and differentiation [161,162]. A very recent literature study published in Science identified that AP1 family member FOS-like 1 (FOSL1) ranks the top key transcription factor to determine the program of CRPC-CSC [119]. In this study, the authors utilized the ATAC-seq from 40 metastatic prostate cancer models (twenty-two patient-derived organoids, six patient-derived xenografts, seven cell lines and five neuroendocrine PCa patients) as inputs to perform clustering consensus analysis based on the top variable chromatin accessible peaks, leading to the identification of four molecular sub-types of CRPC: AR-dependent PCa (CRPC-AR), cancer stem-like PCa (CRPC-SCL), neuroendocrine PCa (CRPC-NE) and Wnt-dependent PCa (CRPC-Wnt). CRPC-SCL, accounting for an estimated 20% of CRPC patients, displays a highly prostate basal stem cell signature compared with other three sub-types and experiences shorter time on AR signaling inhibitor (ARSI) treatment than that of its CRPC-AR counterparts. By integrating ATAC-seq and RNA-seq data, they constructed a regulatory network and finally identified AP-1 family protein FOSL1 as the master regulator for CRPC-SCL. Mechanistically, FOSL1 cooperated with TEAD, YAP and TAZ to control the transcriptional program of CRPC-SCL, which was also confirmed by the overlapped ChIP-seq peaks of these four proteins in SCL models. Indeed, individual depletion of FOSL1, YAP, TAZ and TEAD evidently suppressed the cell growth of SCL models, but had a negligible effect on AR-dependent PCa models. Similar results were also obtained when AP1 inhibitor T-5224 and YAP/TAZ inhibitor verteporfin were tested. In summary, the collective data illustrate that FOSL1 plays as a pioneer factor or a master regulator to control the PCSC transcriptional program, and it will be fascinating to see the clinical outcomes of the AP1 inhibitor in PCa management.

3.10. Others

In addition to the aforementioned signaling pathways, other molecules have been recently reported to influence PCa stemness. Bromodomain adjacent to zinc finger domain protein 2A (BAZ2A), a bromodomain (BRD)-containing protein, recognized histone acetyltransferase p300 (EP300)-mediated H3K14ac marks and suppressed the transcription of differentiation-related genes such as aldehyde oxidase 1 (AOX1), DNA damage-binding protein 1 (DDB1), beta-mannosidase (MANB2) and dystrophin myotonic protein kinase (DMPK), maintaining the stemness stage of PCa [163]. Either BAZ2A mutation or pharmacological inactivation by BAZ2A inhibitor GSK2801 or BAZ2-ICR significantly impaired PCa stem-like features. Although non-coding RNAs, including miRNAs and long non-coding RNAs, have also been reported to be involved in the maintenance of PCSCs, they do not function independently and are therefore excluded from this review.

Glucocorticoid receptor (GR), another steroid receptor member, is also implicated into PCSCs development. Very interestingly, chronic enzalutamide treatment leads to GR upregulation, which replaces AR to transcriptionally regulate AR targeting genes for the survival of enzalutamide-resistant PCa, a new mechanism for PCa cells to escape AR inhibition [164]. Just like the role of AR in PCSCs, GR is also a negative player in PCSC development. A study from Maitland et al. suggested that GR could increase the expression levels of miR-99a and miR-100, which would disrupt the stem cell phenotype of PCa by directly targeting SMARCA5 (an SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5) and SMARCD1 (an SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1) [165]. Together, these results inspire us to combine GR inhibitor with PCSC targeted therapy for the management of enzalutamide-resistant PCa.

4. Potential Clinical Applications of Targeting PCSCs

As discussed, Hedgehog, Wnt, Notch, Hippo, PI3K/AKT, AP1, NF- κ B and JAK-STAT signaling pathways control the survival and homeostasis of PCSCs. To eradicate this fractional population, specific inhibitors towards these signaling pathways have been tested or are being tested in PCa patients/models (Table 2) [128,163,166–199]. For example, gamma-secretase inhibitor RO4929097, for the shutdown of NCID production, was used in combination with bicalutamide to treat PCa patients in 2010 (NCT01200810) [29]. Another clinical trial (NCT01695473) using PI3K/AKT inhibitor BKM120 as a neoadjuvant agent was performed in high risk localized PCa patients [200]. Although these two clinical trials failed, the strategy opens a new window for PCa management by diminishing PCSCs. Additionally, other pathway inhibitors have also been tested in preclinical PCa models: Hedgehog pathway inhibitor sonidegib has been shown to suppress the transcription of stemness-related genes to slow PCa growth [201]; Wnt signaling inhibitors such as 3289-8625, Foxy-5 and OMP-54F28 remarkably hinder PCa growth [178,202,203]; AP1 inhibitor T-5224 and YAP/TAZ inhibitor verteporfin specifically suppress the survival of PCSCs [119]; and JAK-STAT signaling pathway inhibitor ruxolitinib or the combination of fludarabine and niclosamide all show a great inhibitory effect on enzalutamide-resistant PCa models [28].

Immunotherapy is another therapeutic strategy to treat metastatic CRPC patients [204,205]. For instance, prostate specific membrane antigen (PSMA) based CART cells (chimeric antigen receptor T cells) and immune checkpoint inhibitors have been investigated in preclinical PCa models and show beneficial outcomes [206]. Owing to the significance of PCSCs in PCa tumor recurrence, anti-androgen resistance and tumor metastasis, scientists are looking forward to see PCSC-based immunotherapies. In 2020, Chan's group utilized two immunogenic peptides derived from CD44 and epithelial cell adhesion molecule (EpCAM) to educate the isolated dendritic cells, followed by co-culture with cytokine-induced killer cells (CIKs). Interestingly, these adaptive CIKs displayed a tremendous inhibition on PCSCs in vitro and in vivo [207].

Table 2. Prostate cancer stem cells related inhibitors.

Signaling Pathway	Name of Inhibitor	Target	Reference
Notch signaling pathway	PF-03084014	γ -secretase	Cui D, et al., 2015 [128]
	RO4929097	γ -secretase	Du Z, et al., 2021 [166]
	DAPT(GSI-IX)	Notch-1	Cui J, et al., 2018 [167]
	SOX8/RO04929097	Notch-4	Du Z, et al., 2022 [168]
Hedgehog signaling pathway	GDC-0449	SMO	Tong W, et al., 2018 [169]
	GANT-61	GLI	Tong W, et al., 2018 [169]
	vismodegib	SMO	Leao R, et al., 2017 [170]
	itraconazole	SMO	Leao R, et al., 2017 [170]
	sonidegib (LDE-225)	SMO	Burness CB, et al., 2015 [171]
Wnt signaling pathway	LGK974	Porcupine	Ma F, et al., 2016 [172]
	DDK1	LRP5	Browne AJ, et al., 2016 [173]
	DKK3	Frizzled/LRP5/6 complex	Bhattacharyya S, et al., 2019 [174]
	OMP-54F28 (Ipafricept)	Wnt family	Katoh M, et al., 2017 [175]
	OMP-18R5 (Vantictumab)	Frizzled1,2,5,7,8	Katoh M, et al., 2017 [175]
	SFRP	Wnt ligands	Cruz-Hernandez CD, et al., 2020 [176]
	ETC-159 (ETC-1922159)	Porcupine	Katoh M, et al., 2017 [175]
	ICG001 3289-8625	β -actin DVL	Kelsey R, et al., 2017 [177] Schneider JA, et al., 2018 [178]
STAT3 signaling pathway	Napabucasin (BBI608)	STAT3 gene transcription	Zhang Y, et al., 2016 [179]
	Alantolactone (ALT)	STAT3(Tyr705)	Babaei G, et al., 2020 [180]
	EC-70124	STAT3(Tyr705)	Civenni G, et al., 2016 [181]
	ruxolitinib	JAK	Han IH, et al., 2020 [182]
PI3K/AKT signaling pathway	HIF1 α	mTOR	Marhold M, et al., 2015 [183]
	NVP-BEZ235	PI3K and mTOR	Liu G, et al., 2020 [184]
	GSK2636771	P110 β / γ	Sarker D, et al., 2021 [185]
	LY3023414	P110 α / β	Choudhury AD, et al., 2022 [186]
	AZD8186		Hancox U, et al., 2015 [187]
	Apitolisib(GDC-0980), buparlisib	pan-PI3K	Zhou Y, et al., 2015 [188] Armstrong AJ, et al., 2017 [189]
	Ipatasertib MK2206	pan-AKT	Armstrong AJ, et al., 2017 [189] Sweeney C, et al., 2021 [190]
	AZD5363		
	Everolimus		Eule CJ, et al., 2023 [191]
	Temsirolimus		Kruczek K, et al., 2013 [192]
	Ridaforolimus	mTOR	Meulenbeld HJ, et al., 2013 [193]
AZD2014, MLN0128		Li S, et al., 2021 [194] Graham L, et al., 2018 [195]	
NF- κ B signaling pathway	EC-70124	I κ B phosphorylation	Civenni G, et al., 2016 [181]
	Eupatilin	NF- κ B	Serttas R, et al., 2021 [196]
	JSH-23	NF- κ B	Chang KS, et al., 2019 [197]
Hippo signaling pathway	STK3/4	YAP1;TAZ	Schirmer AU, et al., 2022 [198]
	verteporfin	YAP;YAP/TEAD complex	Li Q, et al., 2021 [199]
Others	GSK2801	BAZ2A	
	BAZ2-ICR	BAZ2A	Pena-Hernandez R, et al., 2021 [163]

Although current therapies against PCSCs are not applicable in clinical management owing to various reasons such as drug toxicity, drug stability in the human body and delivery systems, it is still charming for scientists and clinicians to continuously explore in this way.

5. Conclusions and Future Perspectives

To summarize, we conclude that Hedgehog, Wnt, Notch, Hippo, PI3K/AKT, AP1, NF- κ B and JAK-STAT signaling pathways have positive contributions to the evolution

and development of PCSC populations, while AR works negatively. Now, scientists are continuously making efforts to identify other pathways/molecules necessary for PCSC homeostasis. To explore other potential pathways related to PCSCs, we performed Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis on the differential expressed genes (DEGs) between CRPC-AR and CRPC-SCL sub-populations classified by consensus clustering analysis on the SU2C CRPC dataset. Analysis revealed that neuroactive ligand–receptor interactions, MAPK signaling pathway, cytokine–cytokine receptor interactions, calcium signaling pathway and cAMP signaling pathway have potentials to regulate PCSC biology (Figure 3), which requires our experimental validations.

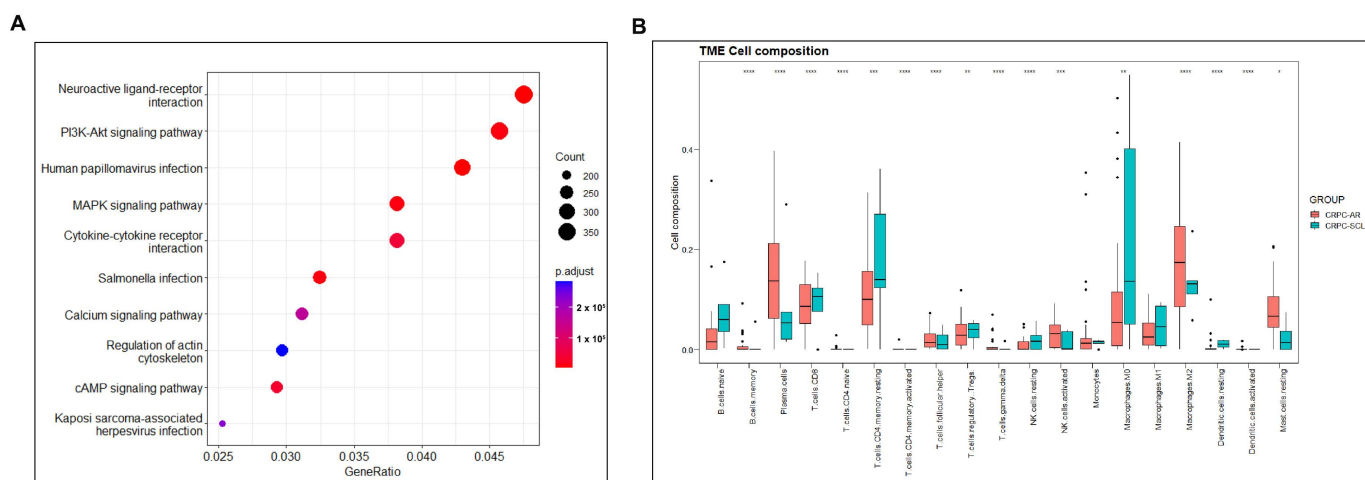


Figure 3. KEGG pathways analysis and immune infiltration analysis of the DEGs between CRPC-AR and CRPC-SCL. (A) KEGG pathway analysis of the DEGs between CRPC-AR and CRPC-SCL. (B) The differential immune cell infiltration between CRPC-AR and CRPC-SCL. * $p < 0.5$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

The PCa micro-environment at least consists of fibroblasts, endothelial cells and immune cells, providing growth support for cancer epithelial cells [208–210]. PCSCs are believed to reside in special micro-environments called niches [211], which undoubtedly has a great impact on PCSC survival and homeostasis. To end this, we performed immune cell infiltration analysis, and the result showed that the population of micro-environmental components is considerably different between CRPC-AR and CRPC-SCL, implying that the survival and expansion of PCSCs are also tightly regulated by the surrounding micro-environment. Again, tremendous efforts on this direction are required.

Author Contributions: Conceptualization, R.W. and R.D.; Formal analysis, Y.Z. and M.J.; Writing—original draft preparation, Y.Z. and T.L.; Writing—review and editing, R.W. All authors have read and agreed to the published version of the manuscript.

Funding: This work was kindly supported by the Sichuan Science and Technology Program (2022YFS0636-B2).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The corresponding author will provide the raw materials if there is a request.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

PCa	prostate cancer
ADT	androgen deprivation therapy
PCSCs	prostate cancer stem cells
AR	androgen receptor
CKs	cytokeratins
CD44	differentiation molecule 44
KRT5	keratin 5
P63	tumor protein 63
PSA	prostate specific antigen
DRE	digital rectal examination
CRPC	castration-resistant prostate cancer
CSCs	cancer stem cells
PSCs	prostate stem cells
NSG	nonobese diabetic scid gamma
PIN	prostatic intraepithelial neoplasia
PTEN	phosphatase and tensin homolog
JAK	Janus kinase
STAT	Signal transducer and activator of transcription
EMT	epithelial–mesenchymal transition
IL-6	Interleukin 6
gp130	glycoprotein 130
MAOA	monoamine oxidative A
HOTAIR	HOX transcript antisense RNA
IL-10	Interleukin 10
LPS	lipopolysaccharide
Kras G12D	kirsten rat sarcoma virus G12D
Ezh2	zeste homolog 2
PRC2	polycomb repressive complex 2
Hh	Hedgehog
SHh	Sonic Hh
IHh	Indian Hh
DHh	Desert Hh
PTCH1	Patched1
SMO	Smoothened
Arrb2	β -Arrestin
Kif3a	kinesin family member 3A
GLI1-3	glioma-associated oncogene homolog 1-3
LRP	lipoprotein receptor-related protein
TCF/LEF	T-cell factor/lymphoid enhancer factor
Axin 2	axis inhibition protein 2
hTERT	human telomerase reverse transcriptase
PHF21B	PHD finger protein 21B
ESM1	endothelial cell-specific molecule 1
ALK	anaplastic lymphoma kinase
NICD	Notch intracellular domain
AKT	protein kinase B
mTORC2	mammalian target of rapamycin complex 2
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells
BMSCs	bone marrow mesenchymal stem cells
BAF	Brahma-associated factor
GSI	γ -secretase inhibitor
IKK	I κ B kinase
BAFFR	B-cell activation factor
RANK	receptor activator for nuclear factor kappa B
LTbR	lymphotoxin b-receptor
TICs	tumor-initiating cells
CXCL12	C-X-C motif chemokine ligand 12

CXCR4	C-X-C motif chemokine receptor 4
PI3K	Phosphoinositide 3-kinase
GPCR	G protein-coupled receptors
RTK	receptor tyrosine kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol 3,4,5-triphosphate
PDK1	phosphoinositide-dependent kinase 1
TSC2	tuberous sclerosis protein 2
FOXO	forkhead box transcription factors of the class O
GSK3b	glycogen synthase kinase 3b
PCaPs	prostate cancer progenitors
MST1/2	mammalian STE20-like protein kinase 1/2
GPCR	G protein coupled receptor
MAP4K	mitogen-activated protein kinase kinase kinase
LATS1/2	large tumor suppressor kinase 1/2
YAP	Yes-associated protein
TAZ	transcriptional co-activator with PDZ-binding motif
PDE5	phosphodiesterase 5
PKGs	protein kinases
EpCAM	epithelial cell adhesion molecule
SOX2	SRY-box transcription factor 2
TRA-1-60	tumor resistance antigen 1-60
OCT-3/4	octamer-binding transforming factor 3/4
BMI-1	B-cell-specific Moloney murine leukemia virus insertion site 1
ABCG-2	ATP binding cassette subfamily G member 2
DVL	Disheveled

References

- Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)] [[PubMed](#)]
- Park, J.W.; Lee, J.K.; Phillips, J.W.; Huang, P.; Cheng, D.; Huang, J.; Witte, O.N. Prostate epithelial cell of origin determines cancer differentiation state in an organoid transformation assay. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 4482–4487. [[CrossRef](#)] [[PubMed](#)]
- Toivanen, R.; Shen, M.M. Prostate organogenesis: Tissue induction, hormonal regulation and cell type specification. *Development* **2017**, *144*, 1382–1398. [[CrossRef](#)] [[PubMed](#)]
- Zhang, D.; Zhao, S.; Li, X.; Kirk, J.S.; Tang, D.G. Prostate Luminal Progenitor Cells in Development and Cancer. *Trends Cancer* **2018**, *4*, 769–783. [[CrossRef](#)] [[PubMed](#)]
- Xie, Q.; Liu, Y.; Cai, T.; Horton, C.; Stefanson, J.; Wang, Z.A. Dissecting cell-type-specific roles of androgen receptor in prostate homeostasis and regeneration through lineage tracing. *Nat. Commun.* **2017**, *8*, 14284. [[CrossRef](#)] [[PubMed](#)]
- Chua, C.W.; Epsi, N.J.; Leung, E.Y.; Xuan, S.; Lei, M.; Li, B.I.; Bergren, S.K.; Hibshoosh, H.; Mitrofanova, A.; Shen, M.M. Differential requirements of androgen receptor in luminal progenitors during prostate regeneration and tumor initiation. *eLife* **2018**, *7*, e28768. [[CrossRef](#)]
- Zhao, H.; Sun, N.; Young, S.R.; Nolley, R.; Santos, J.; Wu, J.C.; Peehl, D.M. Induced pluripotency of human prostatic epithelial cells. *PLoS ONE* **2013**, *8*, e64503. [[CrossRef](#)]
- Su, X.; Long, Q.; Bo, J.; Shi, Y.; Zhao, L.N.; Lin, Y.; Luo, Q.; Ghazanfar, S.; Zhang, C.; Liu, Q.; et al. Mutational and transcriptomic landscapes of a rare human prostate basal cell carcinoma. *Prostate* **2020**, *80*, 508–517. [[CrossRef](#)]
- Henry, G.; Malewska, A.; Mauck, R.; Gahan, J.; Hutchinson, R.; Torrealba, J.; Francis, F.; Roehrborn, C.; Strand, D. Molecular pathogenesis of human prostate basal cell hyperplasia. *Prostate* **2017**, *77*, 1344–1355. [[CrossRef](#)]
- Singh, V.; Manu, V.; Malik, A.; Dutta, V.; Mani, N.S.; Patrikar, S. Diagnostic utility of p63 and alpha-methyl acyl Co A racemase in resolving suspicious foci in prostatic needle biopsy and transurethral resection of prostate specimens. *J. Cancer Res. Ther.* **2014**, *10*, 686–692.
- Watson, P.A.; Arora, V.K.; Sawyers, C.L. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat. Rev. Cancer* **2015**, *15*, 701–711. [[CrossRef](#)] [[PubMed](#)]
- Aurilio, G.; Cimadamore, A.; Mazzucchelli, R.; Lopez-Beltran, A.; Verri, E.; Scarpelli, M.; Massari, F.; Cheng, L.; Santoni, M.; Montironi, R. Androgen Receptor Signaling Pathway in Prostate Cancer: From Genetics to Clinical Applications. *Cells* **2020**, *9*, 2653. [[CrossRef](#)] [[PubMed](#)]
- Frantzi, M.; Culig, Z.; Heidegger, I.; Mokou, M.; Latosinska, A.; Roesch, M.C.; Merseburger, A.S.; Makridakis, M.; Vlahou, A.; Blanca-Pedregosa, A.; et al. Mass Spectrometry-Based Biomarkers to Detect Prostate Cancer: A Multicentric Study Based on Non-Invasive Urine Collection without Prior Digital Rectal Examination. *Cancers* **2023**, *15*, 1166. [[CrossRef](#)] [[PubMed](#)]

14. Prata, F.; Anceschi, U.; Cordelli, E.; Faiella, E.; Civitella, A.; Tuzzolo, P.; Iannuzzi, A.; Ragusa, A.; Esperto, F.; Prata, S.M.; et al. Radiomic Machine-Learning Analysis of Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer: New Combination of Textural and Clinical Features. *Curr. Oncol.* **2023**, *30*, 2021–2031. [[CrossRef](#)] [[PubMed](#)]
15. Miller, K.D.; Nogueira, L.; Devasia, T.; Mariotto, A.B.; Yabroff, K.R.; Jemal, A.; Kramer, J.; Siegel, R.L. Cancer treatment and survivorship statistics, 2022. *CA Cancer J. Clin.* **2022**, *72*, 409–436. [[CrossRef](#)]
16. Crawford, E.D.; Heidenreich, A.; Lawrentschuk, N.; Tombal, B.; Pompeo, A.C.L.; Mendoza-Valdes, A.; Miller, K.; Debruyne, F.M.J.; Klotz, L. Androgen-targeted therapy in men with prostate cancer: Evolving practice and future considerations. *Prostate Cancer Prostatic Dis.* **2019**, *22*, 24–38. [[CrossRef](#)]
17. Galletti, G.; Leach, B.I.; Lam, L.; Tagawa, S.T. Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer. *Cancer Treat. Rev.* **2017**, *57*, 16–27. [[CrossRef](#)]
18. Ferraldeschi, R.; Welti, J.; Luo, J.; Attard, G.; de Bono, J.S. Targeting the androgen receptor pathway in castration-resistant prostate cancer: Progresses and prospects. *Oncogene* **2015**, *34*, 1745–1757. [[CrossRef](#)]
19. Coutinho, I.; Day, T.K.; Tilley, W.D.; Selth, L.A. Androgen receptor signaling in castration-resistant prostate cancer: A lesson in persistence. *Endocr. Relat. Cancer* **2016**, *23*, T179–T197. [[CrossRef](#)]
20. Takeda, D.Y.; Spisak, S.; Seo, J.H.; Bell, C.; O'Connor, E.; Korthauer, K.; Ribli, D.; Csabai, I.; Solymosi, N.; Szallasi, Z.; et al. A Somatic Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer. *Cell* **2018**, *174*, 422–432.e13. [[CrossRef](#)]
21. Rathkopf, D.E.; Smith, M.R.; Ryan, C.J.; Berry, W.R.; Shore, N.D.; Liu, G.; Higano, C.S.; Alumkal, J.J.; Hauke, R.; Tutrone, R.F.; et al. Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide. *Ann. Oncol.* **2017**, *28*, 2264–2271. [[CrossRef](#)] [[PubMed](#)]
22. Schweizer, M.T.; Yu, E.Y. Persistent androgen receptor addiction in castration-resistant prostate cancer. *J. Hematol. Oncol.* **2015**, *8*, 128. [[CrossRef](#)] [[PubMed](#)]
23. Davis, I.D.; Martin, A.J.; Stockler, M.R.; Begbie, S.; Chi, K.N.; Chowdhury, S.; Coskinas, X.; Frydenberg, M.; Hague, W.E.; Horvath, L.G.; et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N. Engl. J. Med.* **2019**, *381*, 121–131. [[CrossRef](#)] [[PubMed](#)]
24. Attard, G.; Murphy, L.; Clarke, N.W.; Cross, W.; Jones, R.J.; Parker, C.C.; Gillissen, S.; Cook, A.; Brawley, C.; Amos, C.L.; et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: A meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet* **2022**, *399*, 447–460. [[CrossRef](#)]
25. Tagawa, S.T.; Ramaswamy, K.; Huang, A.; Mardekian, J.; Schultz, N.M.; Wang, L.; Sandin, R.; Lechpammer, S.; George, D.J. Survival outcomes in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. *Prostate. Cancer Prostatic Dis.* **2021**, *24*, 1032–1040. [[CrossRef](#)]
26. Beer, T.M.; Armstrong, A.J.; Rathkopf, D.E.; Loriot, Y.; Sternberg, C.N.; Higano, C.S.; Iversen, P.; Bhattacharya, S.; Carles, J.; Chowdhury, S.; et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* **2014**, *371*, 424–433. [[CrossRef](#)]
27. Mei, W.; Lin, X.; Kapoor, A.; Gu, Y.; Zhao, K.; Tang, D. The Contributions of Prostate Cancer Stem Cells in Prostate Cancer Initiation and Metastasis. *Cancers* **2019**, *11*, 434. [[CrossRef](#)]
28. Deng, S.; Wang, C.; Wang, Y.; Xu, Y.; Li, X.; Johnson, N.A.; Mukherji, A.; Lo, U.G.; Xu, L.; Gonzalez, J.; et al. Ectopic JAK-STAT activation enables the transition to a stem-like and multilineage state conferring AR-targeted therapy resistance. *Nat. Cancer* **2022**, *3*, 1071–1087. [[CrossRef](#)]
29. Kushwaha, P.P.; Verma, S.; Kumar, S.; Gupta, S. Role of prostate cancer stem-like cells in the development of antiandrogen resistance. *Cancer Drug Resist.* **2022**, *5*, 459–471. [[CrossRef](#)]
30. Yadav, A.K.; Desai, N.S. Cancer Stem Cells: Acquisition, Characteristics, Therapeutic Implications, Targeting Strategies and Future Prospects. *Stem Cell Rev. Rep.* **2019**, *15*, 331–355. [[CrossRef](#)]
31. Barbato, L.; Bocchetti, M.; Di Biase, A.; Regad, T. Cancer Stem Cells and Targeting Strategies. *Cells* **2019**, *8*, 926. [[CrossRef](#)]
32. Lytle, N.K.; Barber, A.G.; Reya, T. Stem cell fate in cancer growth, progression and therapy resistance. *Nat. Rev. Cancer* **2018**, *18*, 669–680. [[CrossRef](#)] [[PubMed](#)]
33. Collins, A.T.; Berry, P.A.; Hyde, C.; Stower, M.J.; Maitland, N.J. Prospective identification of tumorigenic prostate cancer stem cells. *Cancer Res.* **2005**, *65*, 10946–10951. [[CrossRef](#)]
34. Chen, X.; Li, Q.; Liu, X.; Liu, C.; Liu, R.; Rycaj, K.; Zhang, D.; Liu, B.; Jeter, C.; Calhoun-Davis, T.; et al. Defining a Population of Stem-like Human Prostate Cancer Cells That Can Generate and Propagate Castration-Resistant Prostate Cancer. *Clin. Cancer Res.* **2016**, *22*, 4505–4516. [[CrossRef](#)] [[PubMed](#)]
35. Acikgoz, E.; Soner, B.C.; Ozdil, B.; Guven, M. CD133+/CD44+ prostate cancer stem cells exhibit embryo-like behavior patterns. *Acta Histochem.* **2021**, *123*, 151743. [[CrossRef](#)] [[PubMed](#)]
36. Binal, Z.; Acikgoz, E.; Kizilay, F.; Oktem, G.; Altay, B. Cross-talk between ribosome biogenesis, translation, and mTOR in CD133+ 4/CD44+ prostate cancer stem cells. *Clin. Transl. Oncol.* **2020**, *22*, 1040–1048. [[CrossRef](#)]
37. Kalantari, E.; Asgari, M.; Nikpanah, S.; Salarieh, N.; Asadi Lari, M.H.; Madjd, Z. Co-Expression of Putative Cancer Stem Cell Markers CD44 and CD133 in Prostate Carcinomas. *Pathol. Oncol. Res.* **2017**, *23*, 793–802. [[CrossRef](#)]
38. Harris, K.S.; Shi, L.; Foster, B.M.; Mobley, M.E.; Elliott, P.L.; Song, C.J.; Watabe, K.; Langefeld, C.D.; Kerr, B.A. CD117/c-kit defines a prostate CSC-like subpopulation driving progression and TKI resistance. *Sci. Rep.* **2021**, *11*, 1465. [[CrossRef](#)]

39. Aldahish, A.; Kale, A.; Aljameeli, A.; Shah, G.V. Calcitonin induces stem cell-like phenotype in prostate cancer cells. *Endocr. Relat. Cancer* **2019**, *26*, 815–828. [[CrossRef](#)]
40. Naci, D.; Vuori, K.; Aoudjit, F. Alpha2beta1 integrin in cancer development and chemoresistance. *Semin. Cancer Biol.* **2015**, *35*, 145–153. [[CrossRef](#)]
41. Witte, K.E.; Pfitzenmaier, J.; Storm, J.; Lutkemeyer, M.; Wimmer, C.; Schulten, W.; Czaniera, N.; Geisler, M.; Forster, C.; Wilkens, L.; et al. Analysis of Several Pathways for Efficient Killing of Prostate Cancer Stem Cells: A Central Role of NF-kappaB RELA. *Int. J. Mol. Sci.* **2021**, *22*, 8901. [[CrossRef](#)] [[PubMed](#)]
42. Lee, Y.; Yoon, J.; Ko, D.; Yu, M.; Lee, S.; Kim, S. TMPRSS4 promotes cancer stem-like properties in prostate cancer cells through upregulation of SOX2 by SLUG and TWIST1. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 372. [[CrossRef](#)] [[PubMed](#)]
43. Vaddi, P.K.; Stamnes, M.A.; Cao, H.; Chen, S. Elimination of SOX2/OCT4-Associated Prostate Cancer Stem Cells Blocks Tumor Development and Enhances Therapeutic Response. *Cancers* **2019**, *11*, 1331. [[CrossRef](#)] [[PubMed](#)]
44. Huang, J.; Xu, Y.; Wang, F.; Wang, H.; Li, L.; Deng, Y.; Cai, L. Long Noncoding RNA SPRY4-IT1 Modulates Ketamine-Induced Neurotoxicity in Human Embryonic Stem Cell-Derived Neurons through EZH2. *Dev. Neurosci.* **2021**, *43*, 9–17. [[CrossRef](#)]
45. Li, Y.; He, Y.; Butler, W.; Xu, L.; Chang, Y.; Lei, K.; Zhang, H.; Zhou, Y.; Gao, A.C.; Zhang, Q.; et al. Targeting cellular heterogeneity with CXCR2 blockade for the treatment of therapy-resistant prostate cancer. *Sci. Transl. Med.* **2019**, *11*, eaax0428. [[CrossRef](#)]
46. Chatterjee, S.; Behnam Azad, B.; Nimmagadda, S. The intricate role of CXCR4 in cancer. *Adv. Cancer Res.* **2014**, *124*, 31–82.
47. Schafer, C.; Ju, Y.; Tak, Y.; Vazquez, C.; Han, S.J.; Tan, E.; Shay, J.W.; Holmqvist, M.; Danuser, G.; Schopperle, W.M.; et al. TRA-1-60-positive/CD45(low) cells found in the peripheral blood of prostate cancer patients with metastatic disease—A proof-of-concept study. *Heliyon* **2020**, *6*, e03263. [[CrossRef](#)]
48. Wong, A.H.; Tran, T. CD151 in Respiratory Diseases. *Front. Cell Dev. Biol.* **2020**, *8*, 64. [[CrossRef](#)]
49. Wang, X.; Yang, J.Y.; Cai, J.; Zhang, D.J.; Zhao, L.; Luo, L.H.; Xiong, Y.; Zhang, T.; Jin, M. MiR-543/Numb promotes proliferation, metastasis, and stem-like cell traits of prostate cancer cells. *Am. J. Transl. Res.* **2021**, *13*, 617–631.
50. Fujimura, T.; Takahashi, S.; Urano, T.; Takayama, K.; Sugihara, T.; Obinata, D.; Yamada, Y.; Kumagai, J.; Kume, H.; Ouchi, Y.; et al. Expression of androgen and estrogen signaling components and stem cell markers to predict cancer progression and cancer-specific survival in patients with metastatic prostate cancer. *Clin. Cancer Res.* **2014**, *20*, 4625–4635. [[CrossRef](#)]
51. Lou, H.; Li, H.; Huehn, A.R.; Tarasova, N.I.; Saleh, B.; Anderson, S.K.; Dean, M. Genetic and Epigenetic Regulation of the Smoothed Gene (SMO) in Cancer Cells. *Cancers* **2020**, *12*, 2219. [[CrossRef](#)] [[PubMed](#)]
52. Verma, S.; Shankar, E.; Kalayci, F.N.C.; Mukunda, A.; Alassfar, M.; Singh, V.; Chan, E.R.; MacLennan, G.T.; Gupta, S. Androgen Deprivation Induces Transcriptional Reprogramming in Prostate Cancer Cells to Develop Stem Cell-Like Characteristics. *Int. J. Mol. Sci.* **2020**, *21*, 9568. [[CrossRef](#)] [[PubMed](#)]
53. Liu, C.; Sheng, M.; Lin, L.; Li, H.; Guo, S.; Zhang, J.; Chen, G.; Chen, H. NANOG regulates the proliferation of PCSCs via the TGF-beta1/SMAD pathway. *Open Med.* **2020**, *15*, 841–849. [[CrossRef](#)] [[PubMed](#)]
54. Li, Y.; Wang, L.; Liu, J.; Zhang, P.; An, M.; Han, C.; Li, Y.; Guan, X.; Zhang, K. O-GlcNAcylation modulates Bmi-1 protein stability and potential oncogenic function in prostate cancer. *Oncogene* **2017**, *36*, 6293–6305. [[CrossRef](#)]
55. Yoo, Y.A.; Roh, M.; Naseem, A.F.; Lysy, B.; Desouki, M.M.; Unno, K.; Abdulkadir, S.A. Bmi1 marks distinct castration-resistant luminal progenitor cells competent for prostate regeneration and tumour initiation. *Nat. Commun.* **2016**, *7*, 12943. [[CrossRef](#)]
56. Costa, C.D.; Justo, A.A.; Kobayashi, P.E.; Story, M.M.; Palmieri, C.; Laufer Amorim, R.; Fonseca-Alves, C.E. Characterization of OCT3/4, Nestin, NANOG, CD44 and CD24 as stem cell markers in canine prostate cancer. *Int. J. Biochem. Cell Biol.* **2019**, *108*, 21–28. [[CrossRef](#)]
57. Wei, G.J.; Chao, Y.H.; Tung, Y.C.; Wu, T.Y.; Su, Z.Y. A Tangeretin Derivative Inhibits the Growth of Human Prostate Cancer LNCaP Cells by Epigenetically Restoring p21 Gene Expression and Inhibiting Cancer Stem-like Cell Proliferation. *AAPS J.* **2019**, *21*, 86. [[CrossRef](#)]
58. von Lersner, A.; Drogen, L.; Zijlstra, A. Modulation of cell adhesion and migration through regulation of the immunoglobulin superfamily member ALCAM/CD166. *Clin. Exp. Metastasis* **2019**, *36*, 87–95. [[CrossRef](#)]
59. Bansal, N.; Bartucci, M.; Yusuff, S.; Davis, S.; Flaherty, K.; Huselid, E.; Patrizii, M.; Jones, D.; Cao, L.; Sydorenko, N.; et al. BMI-1 Targeting Interferes with Patient-Derived Tumor-Initiating Cell Survival and Tumor Growth in Prostate Cancer. *Clin. Cancer Res.* **2016**, *22*, 6176–6191. [[CrossRef](#)]
60. Erb, H.H.H.; Guggenberger, F.; Santer, F.R.; Culig, Z. Interleukin-4 induces a CD44(high) /CD49b(high) PC3 subpopulation with tumor-initiating characteristics. *J. Cell. Biochem.* **2018**, *119*, 4103–4112. [[CrossRef](#)]
61. Kim, W.T.; Ryu, C.J. Cancer stem cell surface markers on normal stem cells. *BMB Rep.* **2017**, *50*, 285–298. [[CrossRef](#)] [[PubMed](#)]
62. Williamson, S.C.; Hepburn, A.C.; Wilson, L.; Coffey, K.; Ryan-Munden, C.A.; Pal, D.; Leung, H.Y.; Robson, C.N.; Heer, R. Human alpha(2)beta(1)(HI) CD133(+VE) epithelial prostate stem cells express low levels of active androgen receptor. *PLoS ONE* **2012**, *7*, e48944. [[CrossRef](#)] [[PubMed](#)]
63. Lawson, D.A.; Xin, L.; Lukacs, R.U.; Cheng, D.; Witte, O.N. Isolation and functional characterization of murine prostate stem cells. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 181–186. [[CrossRef](#)] [[PubMed](#)]
64. Goldstein, A.S.; Huang, J.; Guo, C.; Garraway, I.P.; Witte, O.N. Identification of a cell of origin for human prostate cancer. *Science* **2010**, *329*, 568–571. [[CrossRef](#)]
65. Choi, N.; Zhang, B.; Zhang, L.; Ittmann, M.; Xin, L. Adult murine prostate basal and luminal cells are self-sustained lineages that can both serve as targets for prostate cancer initiation. *Cancer Cell* **2012**, *21*, 253–265. [[CrossRef](#)]

66. Wang, Z.A.; Mitrofanova, A.; Bergren, S.K.; Abate-Shen, C.; Cardiff, R.D.; Califano, A.; Shen, M.M. Lineage analysis of basal epithelial cells reveals their unexpected plasticity and supports a cell-of-origin model for prostate cancer heterogeneity. *Nat. Cell Biol.* **2013**, *15*, 274–283. [[CrossRef](#)]
67. Wang, Z.A.; Toivanen, R.; Bergren, S.K.; Chambon, P.; Shen, M.M. Luminal cells are favored as the cell of origin for prostate cancer. *Cell Rep.* **2014**, *8*, 1339–1346. [[CrossRef](#)]
68. Kohli, M.; Ho, Y.; Hillman, D.W.; Van Etten, J.L.; Henzler, C.; Yang, R.; Sperger, J.M.; Li, Y.; Tseng, E.; Hon, T.; et al. Androgen Receptor Variant AR-V9 Is Coexpressed with AR-V7 in Prostate Cancer Metastases and Predicts Abiraterone Resistance. *Clin. Cancer Res.* **2017**, *23*, 4704–4715. [[CrossRef](#)]
69. Korpala, M.; Korn, J.M.; Gao, X.; Rakiec, D.P.; Ruddy, D.A.; Doshi, S.; Yuan, J.; Kovats, S.G.; Kim, S.; Cooke, V.G.; et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov.* **2013**, *3*, 1030–1043. [[CrossRef](#)]
70. Liu, G.; Sprenger, C.; Sun, S.; Epilepsia, K.S.; Haugk, K.; Zhang, X.; Coleman, I.; Nelson, P.S.; Plymate, S. AR variant ARv567es induces carcinogenesis in a novel transgenic mouse model of prostate cancer. *Neoplasia* **2013**, *15*, 1009–1017. [[CrossRef](#)]
71. Horning, A.M.; Wang, Y.; Lin, C.K.; Louie, A.D.; Jadhav, R.R.; Hung, C.N.; Wang, C.M.; Lin, C.L.; Kirma, N.B.; Liss, M.A.; et al. Single-Cell RNA-seq Reveals a Subpopulation of Prostate Cancer Cells with Enhanced Cell-Cycle-Related Transcription and Attenuated Androgen Response. *Cancer Res.* **2018**, *78*, 853–864. [[CrossRef](#)]
72. Sanchez, B.G.; Bort, A.; Vara-Ciruelos, D.; Diaz-Laviada, I. Androgen Deprivation Induces Reprogramming of Prostate Cancer Cells to Stem-Like Cells. *Cells* **2020**, *9*, 1441. [[CrossRef](#)]
73. Wu, Z.; Wang, K.; Yang, Z.; Pascal, L.E.; Nelson, J.B.; Takubo, K.; Wipf, P.; Wang, Z. A novel androgen receptor antagonist JJ-450 inhibits enzalutamide-resistant mutant AR(F876L) nuclear import and function. *Prostate* **2020**, *80*, 319–328. [[CrossRef](#)]
74. Denmeade, S.R.; Wang, H.; Agarwal, N.; Smith, D.C.; Schweizer, M.T.; Stein, M.N.; Assikis, V.; Twardowski, P.W.; Flaig, T.W.; Szmulewitz, R.Z.; et al. TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men with Castration-Resistant Metastatic Prostate Cancer. *J. Clin. Oncol.* **2021**, *39*, 1371–1382. [[CrossRef](#)]
75. Antonarakis, E.S.; Lu, C.; Wang, H.; Luber, B.; Nakazawa, M.; Roeser, J.C.; Chen, Y.; Mohammad, T.A.; Chen, Y.; Fedor, H.L.; et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N. Engl. J. Med.* **2014**, *371*, 1028–1038. [[CrossRef](#)]
76. Scher, H.I.; Lu, D.; Schreiber, N.A.; Louw, J.; Graf, R.P.; Vargas, H.A.; Johnson, A.; Jendrisak, A.; Bambury, R.; Danila, D.; et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker with Outcomes and Survival in Castration-Resistant Prostate Cancer. *JAMA Oncol.* **2016**, *2*, 1441–1449. [[CrossRef](#)]
77. Wang, R.; Sun, Y.; Li, L.; Niu, Y.; Lin, W.; Lin, C.; Antonarakis, E.S.; Luo, J.; Yeh, S.; Chang, C. Preclinical Study using Malat1 Small Interfering RNA or Androgen Receptor Splicing Variant 7 Degradation Enhancer ASC-J9((R)) to Suppress Enzalutamide-resistant Prostate Cancer Progression. *Eur. Urol.* **2017**, *72*, 835–844. [[CrossRef](#)]
78. Han, H.; Wang, Y.; Curto, J.; Gurrupu, S.; Laudato, S.; Rumandla, A.; Chakraborty, G.; Wang, X.; Chen, H.; Jiang, Y.; et al. Mesenchymal and stem-like prostate cancer linked to therapy-induced lineage plasticity and metastasis. *Cell Rep.* **2022**, *39*, 110595. [[CrossRef](#)]
79. Nouruzi, S.; Ganguli, D.; Tabrizian, N.; Kobelev, M.; Sivak, O.; Namekawa, T.; Thaper, D.; Baca, S.C.; Freedman, M.L.; Aguda, A.; et al. ASCL1 activates neuronal stem cell-like lineage programming through remodeling of the chromatin landscape in prostate cancer. *Nat. Commun.* **2022**, *13*, 2282. [[CrossRef](#)]
80. Mu, P.; Zhang, Z.; Benelli, M.; Karthaus, W.R.; Hoover, E.; Chen, C.C.; Wongvipat, J.; Ku, S.Y.; Gao, D.; Cao, Z.; et al. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. *Science* **2017**, *355*, 84–88. [[CrossRef](#)]
81. Hu, X.; Li, J.; Fu, M.; Zhao, X.; Wang, W. The JAK/STAT signaling pathway: From bench to clinic. *Signal Transduct. Target. Ther.* **2021**, *6*, 402. [[CrossRef](#)]
82. Herrera, S.C.; Bach, E.A. JAK/STAT signaling in stem cells and regeneration: From Drosophila to vertebrates. *Development* **2019**, *146*, dev167643. [[CrossRef](#)]
83. O’Shea, J.J.; Holland, S.M.; Staudt, L.M. JAKs and STATs in immunity, immunodeficiency, and cancer. *N. Engl. J. Med.* **2013**, *368*, 161–170. [[CrossRef](#)]
84. Seif, F.; Khoshmirasafa, M.; Aazami, H.; Mohsenzadegan, M.; Sedighi, G.; Bahar, M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Commun. Signal* **2017**, *15*, 23. [[CrossRef](#)]
85. Wang, T.; Fahrman, J.F.; Lee, H.; Li, Y.J.; Tripathi, S.C.; Yue, C.; Zhang, C.; Lifshitz, V.; Song, J.; Yuan, Y.; et al. JAK/STAT3-Regulated Fatty Acid beta-Oxidation Is Critical for Breast Cancer Stem Cell Self-Renewal and Chemoresistance. *Cell Metab.* **2018**, *27*, 136–150.e5. [[CrossRef](#)]
86. Wang, X.; Hu, R.; Song, Z.; Zhao, H.; Pan, Z.; Feng, Y.; Yu, Y.; Han, Q.; Zhang, J. Sorafenib combined with STAT3 knockdown triggers ER stress-induced HCC apoptosis and cGAS-STING-mediated anti-tumor immunity. *Cancer Lett.* **2022**, *547*, 215880. [[CrossRef](#)]
87. Rokavec, M.; Oner, M.G.; Li, H.; Jackstadt, R.; Jiang, L.; Lodygin, D.; Kaller, M.; Horst, D.; Ziegler, P.K.; Schwitalla, S.; et al. IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. *J. Clin. Investig.* **2014**, *124*, 1853–1867. [[CrossRef](#)]

88. Jing, Z.; Liu, Q.; Xie, W.; Wei, Y.; Liu, J.; Zhang, Y.; Zuo, W.; Lu, S.; Zhu, Q.; Liu, P. NCAPD3 promotes prostate cancer progression by up-regulating EZH2 and MALAT1 through STAT3 and E2F1. *Cell Signal.* **2022**, *92*, 110265. [[CrossRef](#)]
89. Galoczova, M.; Coates, P.; Vojtesek, B. STAT3, stem cells, cancer stem cells and p63. *Cell Mol. Biol. Lett.* **2018**, *23*, 12. [[CrossRef](#)]
90. Schroeder, A.; Herrmann, A.; Cherryholmes, G.; Kowolik, C.; Buettner, R.; Pal, S.; Yu, H.; Muller-Newen, G.; Jove, R. Loss of androgen receptor expression promotes a stem-like cell phenotype in prostate cancer through STAT3 signaling. *Cancer Res.* **2014**, *74*, 1227–1237. [[CrossRef](#)]
91. Lee, J.L.; Wang, M.J.; Chen, J.Y. Acetylation and activation of STAT3 mediated by nuclear translocation of CD44. *J. Cell Biol.* **2009**, *185*, 949–957. [[CrossRef](#)] [[PubMed](#)]
92. Marotta, L.L.; Almendro, V.; Marusyk, A.; Shipitsin, M.; Schemme, J.; Walker, S.R.; Bloushtain-Qimron, N.; Kim, J.J.; Choudhury, S.A.; Maruyama, R.; et al. The JAK2/STAT3 signaling pathway is required for growth of CD44(+)CD24(-) stem cell-like breast cancer cells in human tumors. *J. Clin. Investig.* **2011**, *121*, 2723–2735. [[CrossRef](#)] [[PubMed](#)]
93. Birnie, R.; Bryce, S.D.; Roome, C.; Dussupt, V.; Droop, A.; Lang, S.H.; Berry, P.A.; Hyde, C.F.; Lewis, J.L.; Stower, M.J.; et al. Gene expression profiling of human prostate cancer stem cells reveals a pro-inflammatory phenotype and the importance of extracellular matrix interactions. *Genome Biol.* **2008**, *9*, R83. [[CrossRef](#)] [[PubMed](#)]
94. Kroon, P.; Berry, P.A.; Stower, M.J.; Rodrigues, G.; Mann, V.M.; Simms, M.; Bhasin, D.; Chettiar, S.; Li, C.; Li, P.K.; et al. JAK-STAT blockade inhibits tumor initiation and clonogenic recovery of prostate cancer stem-like cells. *Cancer Res.* **2013**, *73*, 5288–5298. [[CrossRef](#)]
95. Sorrentino, C.; Ciummo, S.L.; Cipollone, G.; Caputo, S.; Bellone, M.; Di Carlo, E. Interleukin-30/IL27p28 Shapes Prostate Cancer Stem-like Cell Behavior and Is Critical for Tumor Onset and Metastasis. *Cancer Res.* **2018**, *78*, 2654–2668. [[CrossRef](#)]
96. Li, J.; Pu, T.; Yin, L.; Li, Q.; Liao, C.P.; Wu, B.J. MAOA-mediated reprogramming of stromal fibroblasts promotes prostate tumorigenesis and cancer stemness. *Oncogene* **2020**, *39*, 3305–3321. [[CrossRef](#)]
97. Wang, N.; Jiang, Y.; Lv, S.; Wen, H.; Wu, D.; Wei, Q.; Dang, Q. HOTAIR expands the population of prostatic cancer stem-like cells and causes Docetaxel resistance via activating STAT3 signaling. *Aging* **2020**, *12*, 12771–12782. [[CrossRef](#)]
98. Tang, S.; Lian, X.; Cheng, H.; Guo, J.; Ni, D.; Huang, C.; Gu, X.; Meng, H.; Jiang, J.; Li, X. Bacterial Lipopolysaccharide Augmented Malignant Transformation and Promoted the Stemness in Prostate Cancer Epithelial Cells. *J. Inflamm. Res.* **2021**, *14*, 5849–5862. [[CrossRef](#)]
99. Tan, M.H.; Li, J.; Xu, H.E.; Melcher, K.; Yong, E.L. Androgen receptor: Structure, role in prostate cancer and drug discovery. *Acta Pharmacol. Sin.* **2015**, *36*, 3–23. [[CrossRef](#)]
100. Jeter, C.R.; Liu, B.; Lu, Y.; Chao, H.P.; Zhang, D.; Liu, X.; Chen, X.; Li, Q.; Rycaj, K.; Calhoun-Davis, T.; et al. NANOG reprograms prostate cancer cells to castration resistance via dynamically repressing and engaging the AR/FOXA1 signaling axis. *Cell Discov.* **2016**, *2*, 16041. [[CrossRef](#)]
101. Cai, H.; Memarzadeh, S.; Stoyanova, T.; Beharry, Z.; Kraft, A.S.; Witte, O.N. Collaboration of Kras and androgen receptor signaling stimulates EZH2 expression and tumor-propagating cells in prostate cancer. *Cancer Res.* **2012**, *72*, 4672–4681. [[CrossRef](#)] [[PubMed](#)]
102. Doheny, D.; Manore, S.G.; Wong, G.L.; Lo, H.W. Hedgehog Signaling and Truncated GLI1 in Cancer. *Cells* **2020**, *9*, 2114. [[CrossRef](#)] [[PubMed](#)]
103. Lee, H.; Ko, H.W. Ciliary smoothened-mediated noncanonical hedgehog signaling promotes tubulin acetylation. *Biochem. Biophys. Res. Commun.* **2016**, *480*, 574–579. [[CrossRef](#)] [[PubMed](#)]
104. Carballo, G.B.; Honorato, J.R.; de Lopes, G.P.F.; Spohr, T. A highlight on Sonic hedgehog pathway. *Cell Commun. Signal* **2018**, *16*, 11. [[CrossRef](#)] [[PubMed](#)]
105. Clara, J.A.; Monge, C.; Yang, Y.; Takebe, N. Targeting signalling pathways and the immune microenvironment of cancer stem cells—A clinical update. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 204–232. [[CrossRef](#)]
106. Yang, L.; Shi, P.; Zhao, G.; Xu, J.; Peng, W.; Zhang, J.; Zhang, G.; Wang, X.; Dong, Z.; Chen, F.; et al. Targeting cancer stem cell pathways for cancer therapy. *Signal Transduct. Target. Ther.* **2020**, *5*, 8. [[CrossRef](#)]
107. Gu, Y.; Wang, Y.; He, L.; Zhang, J.; Zhu, X.; Liu, N.; Wang, J.; Lu, T.; He, L.; Tian, Y.; et al. Circular RNA circIPO11 drives self-renewal of liver cancer initiating cells via Hedgehog signaling. *Mol. Cancer* **2021**, *20*, 132. [[CrossRef](#)]
108. Chang, H.H.; Chen, B.Y.; Wu, C.Y.; Tsao, Z.J.; Chen, Y.Y.; Chang, C.P.; Yang, C.R.; Lin, D.P. Hedgehog overexpression leads to the formation of prostate cancer stem cells with metastatic property irrespective of androgen receptor expression in the mouse model. *J. Biomed. Sci.* **2011**, *18*, 6. [[CrossRef](#)]
109. Chen, B.Y.; Lin, D.P.; Liu, J.Y.; Chang, H.; Huang, P.H.; Chen, Y.L.; Chang, H.H. A mouse prostate cancer model induced by Hedgehog overexpression. *J. Biomed. Sci.* **2006**, *13*, 373–384. [[CrossRef](#)]
110. Zhang, L.; Li, L.; Jiao, M.; Wu, D.; Wu, K.; Li, X.; Zhu, G.; Yang, L.; Wang, X.; Hsieh, J.T.; et al. Genistein inhibits the stemness properties of prostate cancer cells through targeting Hedgehog-Gli1 pathway. *Cancer Lett.* **2012**, *323*, 48–57. [[CrossRef](#)]
111. Zhan, T.; Rindtorff, N.; Boutros, M. Wnt signaling in cancer. *Oncogene* **2017**, *36*, 1461–1473. [[CrossRef](#)]
112. Katoh, M. Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). *Int. J. Oncol.* **2017**, *51*, 1357–1369. [[CrossRef](#)] [[PubMed](#)]
113. Murillo-Garzon, V.; Kypta, R. WNT signalling in prostate cancer. *Nat. Rev. Urol.* **2017**, *14*, 683–696. [[CrossRef](#)]
114. Zhang, K.; Guo, Y.; Wang, X.; Zhao, H.; Ji, Z.; Cheng, C.; Li, L.; Fang, Y.; Xu, D.; Zhu, H.H.; et al. WNT/beta-Catenin Directs Self-Renewal Symmetric Cell Division of hTERT(high) Prostate Cancer Stem Cells. *Cancer Res.* **2017**, *77*, 2534–2547. [[CrossRef](#)] [[PubMed](#)]

115. Li, Q.; Ye, L.; Guo, W.; Wang, M.; Huang, S.; Peng, X. PHF21B overexpression promotes cancer stem cell-like traits in prostate cancer cells by activating the Wnt/beta-catenin signaling pathway. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 85. [[CrossRef](#)]
116. Pan, K.F.; Lee, W.J.; Chou, C.C.; Yang, Y.C.; Chang, Y.C.; Chien, M.H.; Hsiao, M.; Hua, K.T. Direct interaction of beta-catenin with nuclear ESM1 supports stemness of metastatic prostate cancer. *EMBO J.* **2021**, *40*, e105450. [[CrossRef](#)]
117. Unno, K.; Chalmers, Z.R.; Pamarthy, S.; Vatapalli, R.; Rodriguez, Y.; Lysy, B.; Mok, H.; Sagar, V.; Han, H.; Yoo, Y.A.; et al. Activated ALK Cooperates with N-Myc via Wnt/beta-Catenin Signaling to Induce Neuroendocrine Prostate Cancer. *Cancer Res.* **2021**, *81*, 2157–2170. [[CrossRef](#)]
118. Zhang, Z.; Cheng, L.; Li, J.; Farah, E.; Atallah, N.M.; Pascuzzi, P.E.; Gupta, S.; Liu, X. Inhibition of the Wnt/beta-Catenin Pathway Overcomes Resistance to Enzalutamide in Castration-Resistant Prostate Cancer. *Cancer Res.* **2018**, *78*, 3147–3162. [[CrossRef](#)]
119. Tang, F.; Xu, D.; Wang, S.; Wong, C.K.; Martinez-Fundichely, A.; Lee, C.J.; Cohen, S.; Park, J.; Hill, C.E.; Eng, K.; et al. Chromatin profiles classify castration-resistant prostate cancers suggesting therapeutic targets. *Science* **2022**, *376*, eabe1505. [[CrossRef](#)]
120. O'Brien, R.; Marignol, L. The Notch-1 receptor in prostate tumorigenesis. *Cancer Treat. Rev.* **2017**, *56*, 36–46. [[CrossRef](#)]
121. Zhou, B.; Lin, W.; Long, Y.; Yang, Y.; Zhang, H.; Wu, K.; Chu, Q. Notch signaling pathway: Architecture, disease, and therapeutics. *Signal Transduct. Target. Ther.* **2022**, *7*, 95. [[CrossRef](#)] [[PubMed](#)]
122. Farah, E.; Li, C.; Cheng, L.; Kong, Y.; Lanman, N.A.; Pascuzzi, P.; Lorenz, G.R.; Zhang, Y.; Ahmad, N.; Li, L.; et al. NOTCH signaling is activated in and contributes to resistance in enzalutamide-resistant prostate cancer cells. *J. Biol. Chem.* **2019**, *294*, 8543–8554. [[CrossRef](#)] [[PubMed](#)]
123. Marignol, L.; Rivera-Figueroa, K.; Lynch, T.; Hollywood, D. Hypoxia, notch signalling, and prostate cancer. *Nat. Rev. Urol.* **2013**, *10*, 405–413. [[CrossRef](#)] [[PubMed](#)]
124. Wong, H.Y.; Sheng, Q.; Hesterberg, A.B.; Croessmann, S.; Rios, B.L.; Giri, K.; Jackson, J.; Miranda, A.X.; Watkins, E.; Schaffer, K.R.; et al. Single cell analysis of cribriform prostate cancer reveals cell intrinsic and tumor microenvironmental pathways of aggressive disease. *Nat. Commun.* **2022**, *13*, 6036. [[CrossRef](#)]
125. Guo, Y.; Zhang, K.; Cheng, C.; Ji, Z.; Wang, X.; Wang, M.; Chu, M.; Tang, D.G.; Zhu, H.H.; Gao, W.Q. Numb(-/low) Enriches a Castration-Resistant Prostate Cancer Cell Subpopulation Associated with Enhanced Notch and Hedgehog Signaling. *Clin. Cancer Res.* **2017**, *23*, 6744–6756. [[CrossRef](#)]
126. Cheng, J.W.; Duan, L.X.; Yu, Y.; Wang, P.; Feng, J.L.; Feng, G.Z.; Liu, Y. Bone marrow mesenchymal stem cells promote prostate cancer cell stemness via cell-cell contact to activate the Jagged1/Notch1 pathway. *Cell Biosci.* **2021**, *11*, 87. [[CrossRef](#)] [[PubMed](#)]
127. Hagiwara, M.; Yasumizu, Y.; Yamashita, N.; Rajabi, H.; Fushimi, A.; Long, M.D.; Li, W.; Bhattacharya, A.; Ahmad, R.; Oya, M.; et al. MUC1-C Activates the BAF (mSWI/SNF) Complex in Prostate Cancer Stem Cells. *Cancer Res.* **2021**, *81*, 1111–1122. [[CrossRef](#)]
128. Cui, D.; Dai, J.; Keller, J.M.; Mizokami, A.; Xia, S.; Keller, E.T. Notch Pathway Inhibition Using PF-03084014, a gamma-Secretase Inhibitor (GSI), Enhances the Antitumor Effect of Docetaxel in Prostate Cancer. *Clin. Cancer Res.* **2015**, *21*, 4619–4629. [[CrossRef](#)]
129. Wang, L.; Zi, H.; Luo, Y.; Liu, T.; Zheng, H.; Xie, C.; Wang, X.; Huang, X. Inhibition of Notch pathway enhances the anti-tumor effect of docetaxel in prostate cancer stem-like cells. *Stem Cell Res. Ther.* **2020**, *11*, 258. [[CrossRef](#)]
130. Kaltschmidt, C.; Banz-Jansen, C.; Benhidjeb, T.; Beshay, M.; Forster, C.; Greiner, J.; Hamelmann, E.; Jorch, N.; Mertzluft, F.; Pfitzenmaier, J.; et al. A Role for NF-kappaB in Organ Specific Cancer and Cancer Stem Cells. *Cancers* **2019**, *11*, 655. [[CrossRef](#)]
131. Kaltschmidt, B.; Witte, K.E.; Greiner, J.F.W.; Weissinger, F.; Kaltschmidt, C. Targeting NF-kappaB Signaling in Cancer Stem Cells: A Narrative Review. *Biomedicines* **2022**, *10*, 261. [[CrossRef](#)] [[PubMed](#)]
132. Taniguchi, K.; Karin, M. NF-kappaB, inflammation, immunity and cancer: Coming of age. *Nat. Rev. Immunol.* **2018**, *18*, 309–324. [[CrossRef](#)] [[PubMed](#)]
133. Zhang, Q.; Lenardo, M.J.; Baltimore, D. 30 Years of NF-kappaB: A Blossoming of Relevance to Human Pathobiology. *Cell* **2017**, *168*, 37–57. [[CrossRef](#)]
134. Sun, S.C. The non-canonical NF-kappaB pathway in immunity and inflammation. *Nat. Rev. Immunol.* **2017**, *17*, 545–558. [[CrossRef](#)] [[PubMed](#)]
135. Yu, H.; Lin, L.; Zhang, Z.; Zhang, H.; Hu, H. Targeting NF-kappaB pathway for the therapy of diseases: Mechanism and clinical study. *Signal Transduct. Target. Ther.* **2020**, *5*, 209. [[CrossRef](#)] [[PubMed](#)]
136. Rajasekhar, V.K.; Studer, L.; Gerald, W.; Socci, N.D.; Scher, H.I. Tumour-initiating stem-like cells in human prostate cancer exhibit increased NF-kappaB signalling. *Nat. Commun.* **2011**, *2*, 162. [[CrossRef](#)]
137. Jung, Y.; Cackowski, F.C.; Yumoto, K.; Decker, A.M.; Wang, J.; Kim, J.K.; Lee, E.; Wang, Y.; Chung, J.S.; Gursky, A.M.; et al. CXCL12gamma Promotes Metastatic Castration-Resistant Prostate Cancer by Inducing Cancer Stem Cell and Neuroendocrine Phenotypes. *Cancer Res.* **2018**, *78*, 2026–2039. [[CrossRef](#)]
138. Nouri, M.; Massah, S.; Caradec, J.; Lubik, A.A.; Li, N.; Truong, S.; Lee, A.R.; Fazli, L.; Ramnarine, V.R.; Lovnicki, J.M.; et al. Transient Sox9 Expression Facilitates Resistance to Androgen-Targeted Therapy in Prostate Cancer. *Clin. Cancer Res.* **2020**, *26*, 1678–1689. [[CrossRef](#)]
139. Hua, H.; Zhang, H.; Chen, J.; Wang, J.; Liu, J.; Jiang, Y. Targeting Akt in cancer for precision therapy. *J. Hematol. Oncol.* **2021**, *14*, 128. [[CrossRef](#)]
140. Lien, E.C.; Dibble, C.C.; Toker, A. PI3K signaling in cancer: Beyond AKT. *Curr. Opin. Cell Biol.* **2017**, *45*, 62–71. [[CrossRef](#)]
141. Yuan, D.; Yang, Z.; Chen, Y.; Li, S.; Tan, B.; Yu, Q. Hypoxia-induced SPOP attenuates the mobility of trophoblast cells through inhibition of the PI3K/AKT/GSK3beta pathway. *Cell Biol. Int.* **2021**, *45*, 599–611. [[CrossRef](#)]

142. Alzahrani, A.S. PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. *Semin. Cancer Biol.* **2019**, *59*, 125–132. [[CrossRef](#)]
143. Goldbraikh, D.; Neufeld, D.; Eid-Mutlak, Y.; Lasry, I.; Gilda, J.E.; Parnis, A.; Cohen, S. USP1 deubiquitinates Akt to inhibit PI3K-Akt-FoxO signaling in muscle during prolonged starvation. *EMBO Rep.* **2020**, *21*, e48791. [[CrossRef](#)] [[PubMed](#)]
144. Chiang, Y.J.; Liao, W.T.; Ho, K.C.; Wang, S.H.; Chen, Y.G.; Ho, C.L.; Huang, S.F.; Shih, L.Y.; Yang-Yen, H.F.; Yen, J.J. CBAP modulates Akt-dependent TSC2 phosphorylation to promote Rheb-mTORC1 signaling and growth of T-cell acute lymphoblastic leukemia. *Oncogene* **2019**, *38*, 1432–1447. [[CrossRef](#)] [[PubMed](#)]
145. Jamaspishvili, T.; Berman, D.M.; Ross, A.E.; Scher, H.I.; De Marzo, A.M.; Squire, J.A.; Lotan, T.L. Clinical implications of PTEN loss in prostate cancer. *Nat. Rev. Urol.* **2018**, *15*, 222–234. [[CrossRef](#)] [[PubMed](#)]
146. Dubrovska, A.; Kim, S.; Salamone, R.J.; Walker, J.R.; Maira, S.M.; García-Echeverría, C.; Schultz, P.G.; Reddy, V.A. The role of PTEN/Akt/PI3K signaling in the maintenance and viability of prostate cancer stem-like cell populations. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 268–273. [[CrossRef](#)]
147. Yu, J.; Qi, H.; Wang, Z.; Zhang, Z.; Song, E.; Song, W.; An, R. RAB3D, upregulated by aryl hydrocarbon receptor (AhR), promotes the progression of prostate cancer by activating the PI3K/AKT signaling pathway. *Cell Biol. Int.* **2022**, *46*, 2246–2256. [[CrossRef](#)]
148. Ellis, L.; Ku, S.Y.; Ramakrishnan, S.; Lasorsa, E.; Azabdaftari, G.; Godoy, A.; Pili, R. Combinatorial antitumor effect of HDAC and the PI3K-Akt-mTOR pathway inhibition in a Pten deficient model of prostate cancer. *Oncotarget* **2013**, *4*, 2225–2236. [[CrossRef](#)]
149. Chang, L.; Graham, P.H.; Hao, J.; Ni, J.; Bucci, J.; Cozzi, P.J.; Kearsley, J.H.; Li, Y. Acquisition of epithelial-mesenchymal transition and cancer stem cell phenotypes is associated with activation of the PI3K/Akt/mTOR pathway in prostate cancer radioresistance. *Cell Death Dis.* **2013**, *4*, e875. [[CrossRef](#)]
150. Jansson, K.H.; Tucker, J.B.; Stahl, L.E.; Simmons, J.K.; Fuller, C.; Beshiri, M.L.; Agarwal, S.; Fang, L.; Hynes, P.G.; Alilun, A.N.; et al. High-throughput screens identify HSP90 inhibitors as potent therapeutics that target inter-related growth and survival pathways in advanced prostate cancer. *Sci. Rep.* **2018**, *8*, 17239. [[CrossRef](#)]
151. Zheng, Y.; Pan, D. The Hippo Signaling Pathway in Development and Disease. *Dev. Cell* **2019**, *50*, 264–282. [[CrossRef](#)] [[PubMed](#)]
152. Mohajan, S.; Jaiswal, P.K.; Vatanmakarian, M.; Yousefi, H.; Sankaralingam, S.; Alahari, S.K.; Koul, S.; Koul, H.K. Hippo pathway: Regulation, deregulation and potential therapeutic targets in cancer. *Cancer Lett.* **2021**, *507*, 112–123. [[CrossRef](#)] [[PubMed](#)]
153. Meng, Z.; Moroishi, T.; Mottier-Pavie, V.; Plouffe, S.W.; Hansen, C.G.; Hong, A.W.; Park, H.W.; Mo, J.S.; Lu, W.; Lu, S.; et al. MAP4K family kinases act in parallel to MST1/2 to activate LATS1/2 in the Hippo pathway. *Nat. Commun.* **2015**, *6*, 8357. [[CrossRef](#)] [[PubMed](#)]
154. Huh, H.D.; Kim, D.H.; Jeong, H.S.; Park, H.W. Regulation of TEAD Transcription Factors in Cancer Biology. *Cells* **2019**, *8*, 600. [[CrossRef](#)]
155. Lin, K.C.; Moroishi, T.; Meng, Z.; Jeong, H.S.; Plouffe, S.W.; Sekido, Y.; Han, J.; Park, H.W.; Guan, K.L. Regulation of Hippo pathway transcription factor TEAD by p38 MAPK-induced cytoplasmic translocation. *Nat. Cell Biol.* **2017**, *19*, 996–1002. [[CrossRef](#)]
156. Koo, J.H.; Guan, K.L. Interplay between YAP/TAZ and Metabolism. *Cell Metab.* **2018**, *28*, 196–206. [[CrossRef](#)]
157. Moroishi, T.; Hansen, C.G.; Guan, K.L. The emerging roles of YAP and TAZ in cancer. *Nat. Rev. Cancer* **2015**, *15*, 73–79. [[CrossRef](#)] [[PubMed](#)]
158. Salem, O.; Hansen, C.G. The Hippo Pathway in Prostate Cancer. *Cells* **2019**, *8*, 370. [[CrossRef](#)]
159. Liu, N.; Mei, L.; Fan, X.; Tang, C.; Ji, X.; Hu, X.; Shi, W.; Qian, Y.; Hussain, M.; Wu, J.; et al. Phosphodiesterase 5/protein kinase G signal governs stemness of prostate cancer stem cells through Hippo pathway. *Cancer Lett.* **2016**, *378*, 38–50. [[CrossRef](#)]
160. Lai, C.J.; Lin, C.Y.; Liao, W.Y.; Hour, T.C.; Wang, H.D.; Chuu, C.P. CD44 Promotes Migration and Invasion of Docetaxel-Resistant Prostate Cancer Cells Likely via Induction of Hippo-Yap Signaling. *Cells* **2019**, *8*, 295. [[CrossRef](#)]
161. Casalino, L.; Talotta, F.; Cimmino, A.; Verde, P. The Fra-1/AP-1 Oncoprotein: From the “Undruggable” Transcription Factor to Therapeutic Targeting. *Cancers* **2022**, *14*, 1480. [[CrossRef](#)] [[PubMed](#)]
162. Koo, J.H.; Plouffe, S.W.; Meng, Z.; Lee, D.H.; Yang, D.; Lim, D.S.; Wang, C.Y.; Guan, K.L. Induction of AP-1 by YAP/TAZ contributes to cell proliferation and organ growth. *Genes Dev.* **2020**, *34*, 72–86. [[CrossRef](#)] [[PubMed](#)]
163. Pena-Hernandez, R.; Aprigliano, R.; Frommel, S.C.; Pietrzak, K.; Steiger, S.; Roganowicz, M.; Lerra, L.; Bizzarro, J.; Santoro, R. BAZ2A-mediated repression via H3K14ac-marked enhancers promotes prostate cancer stem cells. *EMBO Rep.* **2021**, *22*, e53014. [[CrossRef](#)]
164. Arora, V.K.; Schenkein, E.; Murali, R.; Subudhi, S.K.; Wongvipat, J.; Balbas, M.D.; Shah, N.; Cai, L.; Efstathiou, E.; Logothetis, C.; et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell* **2013**, *155*, 1309–1322. [[CrossRef](#)]
165. Rane, J.K.; Erb, H.H.; Nappo, G.; Mann, V.M.; Simms, M.S.; Collins, A.T.; Visakorpi, T.; Maitland, N.J. Inhibition of the glucocorticoid receptor results in an enhanced miR-99a/100-mediated radiation response in stem-like cells from human prostate cancers. *Oncotarget* **2016**, *7*, 51965–51980. [[CrossRef](#)] [[PubMed](#)]
166. Du, Z.; Li, L.; Sun, W.; Zhu, P.; Cheng, S.; Yang, X.; Luo, C.; Yu, X.; Wu, X. Systematic Evaluation for the Influences of the SOX17/Notch Receptor Family Members on Reversing Enzalutamide Resistance in Castration-Resistant Prostate Cancer Cells. *Front. Oncol.* **2021**, *11*, 607291. [[CrossRef](#)]
167. Cui, J.; Wang, Y.; Dong, B.; Qin, L.; Wang, C.; Zhou, P.; Wang, X.; Xu, H.; Xue, W.; Fang, Y.X.; et al. Pharmacological inhibition of the Notch pathway enhances the efficacy of androgen deprivation therapy for prostate cancer. *Int. J. Cancer* **2018**, *143*, 645–656. [[CrossRef](#)]

168. Du, Z.; Chen, X.; Zhu, P.; Sun, W.; Lv, Q.; Cheng, S.; Yang, X.; Yu, X. SOX8 Knockdown Overcomes Enzalutamide Resistance in Castration-Resistant Prostate Cancer by Inhibiting the Notch Signaling Pathway. *BioMed Res. Int.* **2022**, *2022*, 9235837. [[CrossRef](#)]
169. Tong, W.; Qiu, L.; Qi, M.; Liu, J.; Hu, K.; Lin, W.; Huang, Y.; Fu, J. GANT-61 and GDC-0449 induce apoptosis of prostate cancer stem cells through a GLI-dependent mechanism. *J. Cell. Biochem.* **2018**, *119*, 3641–3652. [[CrossRef](#)]
170. Leao, R.; Domingos, C.; Figueiredo, A.; Hamilton, R.; Tabori, U.; Castelo-Branco, P. Cancer Stem Cells in Prostate Cancer: Implications for Targeted Therapy. *Urol. Int.* **2017**, *99*, 125–136. [[CrossRef](#)]
171. Burness, C.B. Sonidegib: First Global Approval. *Drugs* **2015**, *75*, 1559–1566. [[CrossRef](#)] [[PubMed](#)]
172. Ma, F.; Ye, H.; He, H.H.; Gerrin, S.J.; Chen, S.; Tanenbaum, B.A.; Cai, C.; Sowalsky, A.G.; He, L.; Wang, H.; et al. SOX9 drives WNT pathway activation in prostate cancer. *J. Clin. Investig.* **2016**, *126*, 1745–1758. [[CrossRef](#)] [[PubMed](#)]
173. Browne, A.J.; Gobel, A.; Thiele, S.; Hofbauer, L.C.; Rauner, M.; Rachner, T.D. p38 MAPK regulates the Wnt inhibitor Dickkopf-1 in osteotropic prostate cancer cells. *Cell Death Dis.* **2016**, *7*, e2119. [[CrossRef](#)] [[PubMed](#)]
174. Bhattacharyya, S.; Feferman, L.; Tobacman, J.K. Dihydrotestosterone inhibits arylsulfatase B and Dickkopf Wnt signaling pathway inhibitor (DKK)-3 leading to enhanced Wnt signaling in prostate epithelium in response to stromal Wnt3A. *Prostate* **2019**, *79*, 689–700. [[CrossRef](#)]
175. Katoh, M.; Katoh, M. Molecular genetics and targeted therapy of WNT-related human diseases (Review). *Int. J. Mol. Med.* **2017**, *40*, 587–606. [[CrossRef](#)]
176. Cruz-Hernandez, C.D.; Cruz-Burgos, M.; Cortes-Ramirez, S.A.; Losada-Garcia, A.; Camacho-Arroyo, I.; Garcia-Lopez, P.; Langley, E.; Gonzalez-Covarrubias, V.; Llaguno-Munive, M.; Albino-Sanchez, M.E.; et al. SFRP1 increases TMPRSS2-ERG expression promoting neoplastic features in prostate cancer in vitro and in vivo. *Cancer Cell Int.* **2020**, *20*, 312. [[CrossRef](#)]
177. Kelsey, R. Prostate cancer: Foxy-5 in prostate cancer model. *Nat. Rev. Urol.* **2017**, *14*, 638. [[CrossRef](#)]
178. Schneider, J.A.; Logan, S.K. Revisiting the role of Wnt/beta-catenin signaling in prostate cancer. *Mol. Cell. Endocrinol.* **2018**, *462*, 3–8. [[CrossRef](#)]
179. Zhang, Y.; Jin, Z.; Zhou, H.; Ou, X.; Xu, Y.; Li, H.; Liu, C.; Li, B. Suppression of prostate cancer progression by cancer cell stemness inhibitor napabucasin. *Cancer Med.* **2016**, *5*, 1251–1258. [[CrossRef](#)]
180. Babaei, G.; Khadem Ansari, M.H.; Aziz, S.G.; Bazl, M.R. Alantolactone inhibits stem-like cell phenotype, chemoresistance and metastasis in PC3 cells through STAT3 signaling pathway. *Res. Pharm. Sci.* **2020**, *15*, 551–562.
181. Civenni, G.; Longoni, N.; Costales, P.; Dallavalle, C.; Garcia Inclan, C.; Albino, D.; Nunez, L.E.; Moris, F.; Carbone, G.M.; Catapano, C.V. EC-70124, a Novel Glycosylated Indolocarbazole Multikinase Inhibitor, Reverts Tumorigenic and Stem Cell Properties in Prostate Cancer by Inhibiting STAT3 and NF-kappaB. *Mol. Cancer Ther.* **2016**, *15*, 806–818. [[CrossRef](#)] [[PubMed](#)]
182. Han, I.H.; Song, H.O.; Ryu, J.S. IL-6 produced by prostate epithelial cells stimulated with *Trichomonas vaginalis* promotes proliferation of prostate cancer cells by inducing M2 polarization of THP-1-derived macrophages. *PLoS Negl. Trop. Dis.* **2020**, *14*, e0008126. [[CrossRef](#)]
183. Marhold, M.; Tomasich, E.; El-Gazzar, A.; Heller, G.; Spittler, A.; Horvat, R.; Krainer, M.; Horak, P. HIF1alpha Regulates mTOR Signaling and Viability of Prostate Cancer Stem Cells. *Mol. Cancer Res.* **2015**, *13*, 556–564. [[CrossRef](#)] [[PubMed](#)]
184. Liu, G.; Jin, Z.; Lu, X. Differential Targeting of Gr-MDSCs, T Cells and Prostate Cancer Cells by Dactolisib and Dasatinib. *Int. J. Mol. Sci.* **2020**, *21*, 2337. [[CrossRef](#)] [[PubMed](#)]
185. Sarker, D.; Dawson, N.A.; Aparicio, A.M.; Dorff, T.B.; Pantuck, A.J.; Vaishampayan, U.N.; Henson, L.; Vasist, L.; Roy-Ghanta, S.; Gorczyca, M.; et al. A Phase I, Open-Label, Dose-Finding Study of GSK2636771, a PI3Kbeta Inhibitor, Administered with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin. Cancer Res.* **2021**, *27*, 5248–5257. [[CrossRef](#)]
186. Choudhury, A.D. PTEN-PI3K pathway alterations in advanced prostate cancer and clinical implications. *Prostate* **2022**, *82* (Suppl. 1), S60–S72. [[CrossRef](#)]
187. Hancox, U.; Cosulich, S.; Hanson, L.; Trigwell, C.; Lenaghan, C.; Ellston, R.; Dry, H.; Crafter, C.; Barlaam, B.; Fitzek, M.; et al. Inhibition of PI3Kbeta signaling with AZD8186 inhibits growth of PTEN-deficient breast and prostate tumors alone and in combination with docetaxel. *Mol. Cancer Ther.* **2015**, *14*, 48–58. [[CrossRef](#)]
188. Zhou, Y.; Yang, J.; Zhang, R.; Kopecek, J. Combination therapy of prostate cancer with HPMa copolymer conjugates containing PI3K/mTOR inhibitor and docetaxel. *Eur. J. Pharm. Biopharm.* **2015**, *89*, 107–115. [[CrossRef](#)]
189. Armstrong, A.J.; Halabi, S.; Healy, P.; Alumkal, J.J.; Winters, C.; Kephart, J.; Bitting, R.L.; Hobbs, C.; Soleau, C.F.; Beer, T.M.; et al. Phase II trial of the PI3 kinase inhibitor buparlisib (BKM-120) with or without enzalutamide in men with metastatic castration resistant prostate cancer. *Eur. J. Cancer* **2017**, *81*, 228–236. [[CrossRef](#)]
190. Sweeney, C.; Bracarda, S.; Sternberg, C.N.; Chi, K.N.; Olmos, D.; Sandhu, S.; Massard, C.; Matsubara, N.; Alekseev, B.; Parnis, F.; et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* **2021**, *398*, 131–142. [[CrossRef](#)]
191. Eule, C.J.; Flaig, T.W.; Wong, K.; Graf, R.; Lam, E.T. Effectiveness and durability of benefit of mTOR inhibitors in a real-world cohort of patients with metastatic prostate cancer and PI3K pathway alterations. *Prostate Cancer Prostatic Dis.* **2023**, *26*, 188–193. [[CrossRef](#)] [[PubMed](#)]
192. Kruczek, K.; Ratterman, M.; Tolzien, K.; Sulo, S.; Lestingi, T.M.; Nabhan, C. A phase II study evaluating the toxicity and efficacy of single-agent temsirolimus in chemotherapy-naive castration-resistant prostate cancer. *Br. J. Cancer.* **2013**, *109*, 1711–1716. [[CrossRef](#)] [[PubMed](#)]

193. Meulenbeld, H.J.; de Bono, J.S.; Tagawa, S.T.; Whang, Y.E.; Li, X.; Heath, K.H.; Zandvliet, A.S.; Ebbinghaus, S.W.; Hudes, G.R.; de Wit, R. Tolerability, safety and pharmacokinetics of ridaforolimus in combination with bicalutamide in patients with asymptomatic, metastatic castration-resistant prostate cancer (CRPC). *Cancer Chemother. Pharmacol.* **2013**, *72*, 909–916. [[CrossRef](#)]
194. Li, S.; Sheng, J.; Liu, Z.; Fan, Y.; Zhang, C.; Lv, T.; Hu, S.; Jin, J.; Yu, W.; Song, Y. Potent antitumour of the mTORC1/2 dual inhibitor AZD2014 in docetaxel-sensitive and docetaxel-resistant castration-resistant prostate cancer cells. *J. Cell. Mol. Med.* **2021**, *25*, 2436–2449. [[CrossRef](#)] [[PubMed](#)]
195. Graham, L.; Banda, K.; Torres, A.; Carver, B.S.; Chen, Y.; Pisano, K.; Shelkey, G.; Curley, T.; Scher, H.I.; Lotan, T.L.; et al. A phase II study of the dual mTOR inhibitor MLN0128 in patients with metastatic castration resistant prostate cancer. *Investig. New Drugs* **2018**, *36*, 458–467. [[CrossRef](#)] [[PubMed](#)]
196. Serttas, R.; Koroglu, C.; Erdogan, S. Eupatilin Inhibits the Proliferation and Migration of Prostate Cancer Cells through Modulation of PTEN and NF-kappaB Signaling. *Anticancer Agents Med. Chem.* **2021**, *21*, 372–382. [[CrossRef](#)]
197. Chang, K.S.; Tsui, K.H.; Lin, Y.H.; Hou, C.P.; Feng, T.H.; Juang, H.H. Migration and Invasion Enhancer 1 Is an NF-kB-Inducing Gene Enhancing the Cell Proliferation and Invasion Ability of Human Prostate Carcinoma Cells In Vitro and In Vivo. *Cancers* **2019**, *11*, 1486. [[CrossRef](#)]
198. Schirmer, A.U.; Driver, L.M.; Zhao, M.T.; Wells, C.I.; Pickett, J.E.; O’Byrne, S.N.; Eduful, B.J.; Yang, X.; Howard, L.; You, S.; et al. Non-canonical role of Hippo tumor suppressor serine/threonine kinase 3 STK3 in prostate cancer. *Mol. Ther.* **2022**, *30*, 485–500. [[CrossRef](#)]
199. Li, Q.; Wang, M.; Hu, Y.; Zhao, E.; Li, J.; Ren, L.; Wang, M.; Xu, Y.; Liang, Q.; Zhang, D.; et al. MYBL2 disrupts the Hippo-YAP pathway and confers castration resistance and metastatic potential in prostate cancer. *Theranostics* **2021**, *11*, 5794–5812. [[CrossRef](#)]
200. Pietzak, E.J.; Eastham, J.A. Neoadjuvant Treatment of High-Risk, Clinically Localized Prostate Cancer Prior to Radical Prostatectomy. *Curr. Urol. Rep.* **2016**, *17*, 37. [[CrossRef](#)]
201. Ross, A.E.; Hughes, R.M.; Glavaris, S.; Ghabili, K.; He, P.; Anders, N.M.; Harb, R.; Tosoian, J.J.; Marchionni, L.; Schaeffer, E.M.; et al. Pharmacodynamic and pharmacokinetic neoadjuvant study of hedgehog pathway inhibitor Sonidegib (LDE-225) in men with high-risk localized prostate cancer undergoing prostatectomy. *Oncotarget* **2017**, *8*, 104182–104192. [[CrossRef](#)] [[PubMed](#)]
202. Le, P.N.; McDermott, J.D.; Jimeno, A. Targeting the Wnt pathway in human cancers: Therapeutic targeting with a focus on OMP-54F28. *Pharmacol. Ther.* **2015**, *146*, 1–11. [[CrossRef](#)] [[PubMed](#)]
203. Canesin, G.; Evans-Axelsson, S.; Hellsten, R.; Krzyzanowska, A.; Prasad, C.P.; Bjartell, A.; Andersson, T. Treatment with the WNT5A-mimicking peptide Foxy-5 effectively reduces the metastatic spread of WNT5A-low prostate cancer cells in an orthotopic mouse model. *PLoS ONE* **2017**, *12*, e0184418. [[CrossRef](#)] [[PubMed](#)]
204. Zurowski, D.; Patel, S.; Hui, D.; Ka, M.; Hernandez, C.; Love, A.C.; Lin, B.; Moore, A.; Chan, L.L. High-throughput method to analyze the cytotoxicity of CAR-T Cells in a 3D tumor spheroid model using image cytometry. *SLAS Discov.* **2023**, *in press*. [[CrossRef](#)] [[PubMed](#)]
205. Gamat, M.; McNeel, D.G. Androgen deprivation and immunotherapy for the treatment of prostate cancer. *Endocr. Relat. Cancer* **2017**, *24*, T297–T310. [[CrossRef](#)]
206. Deegen, P.; Thomas, O.; Nolan-Stevaux, O.; Li, S.; Wahl, J.; Bogner, P.; Aeffner, F.; Friedrich, M.; Liao, M.Z.; Matthes, K.; et al. The PSMA-targeting Half-life Extended BiTE Therapy AMG 160 has Potent Antitumor Activity in Preclinical Models of Metastatic Castration-resistant Prostate Cancer. *Clin. Cancer Res.* **2021**, *27*, 2928–2937. [[CrossRef](#)]
207. Wang, Z.; Li, Y.; Wang, Y.; Wu, D.; Lau, A.H.Y.; Zhao, P.; Zou, C.; Dai, Y.; Chan, F.L. Targeting prostate cancer stem-like cells by an immunotherapeutic platform based on immunogenic peptide-sensitized dendritic cells-cytokine-induced killer cells. *Stem Cell Res. Ther.* **2020**, *11*, 123. [[CrossRef](#)]
208. Kang, J.; La Manna, F.; Bonollo, F.; Sampson, N.; Alberts, I.L.; Mingels, C.; Afshar-Oromieh, A.; Thalmann, G.N.; Karkampouna, S. Tumor microenvironment mechanisms and bone metastatic disease progression of prostate cancer. *Cancer Lett.* **2022**, *530*, 156–169. [[CrossRef](#)]
209. Kfoury, Y.; Baryawno, N.; Severe, N.; Mei, S.; Gustafsson, K.; Hirz, T.; Brouse, T.; Scadden, E.W.; Igoalkina, A.A.; Kokkaliaris, K.; et al. Human prostate cancer bone metastases have an actionable immunosuppressive microenvironment. *Cancer Cell* **2021**, *39*, 1464–1478.e8. [[CrossRef](#)]
210. Tang, Q.; Cheng, B.; Dai, R.; Wang, R. The Role of Androgen Receptor in Cross Talk Between Stromal Cells and Prostate Cancer Epithelial Cells. *Front. Cell Dev. Biol.* **2021**, *9*, 729498. [[CrossRef](#)]
211. Brown, T.J.; James, V. The Role of Extracellular Vesicles in the Development of a Cancer Stem Cell Microenvironment Niche and Potential Therapeutic Targets: A Systematic Review. *Cancers* **2021**, *13*, 2435. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.