Review

The PI3K-AKT-mTOR Pathway and Prostate Cancer: At the Crossroads of AR, MAPK, and WNT Signaling

Boris Y. Shorning, Manisha S. Dass, Matthew J. Smalley and Helen B. Pearson *

The European Cancer Stem Cell Research Institute, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, Wales, UK; ShorningB@cardiff.ac.uk (B.Y.S.); DassMS@cardiff.ac.uk (M.S.D.); SmalleyMJ@cardiff.ac.uk (M.J.S.)

* Correspondence: PearsonH2@cardiff.ac.uk

Received: 1 June 2020; Accepted: 22 June 2020; Published: 25 June 2020

Abstract: Oncogenic activation of the phosphatidylinositol-3-kinase (PI3K), protein kinase B (PKB/AKT), and mammalian target of rapamycin (mTOR) pathway is a frequent event in prostate cancer that facilitates tumor formation, disease progression and therapeutic resistance. Recent discoveries indicate that the complex crosstalk between the PI3K-AKT-mTOR pathway and multiple interacting cell signaling cascades can further promote prostate cancer progression and influence the sensitivity of prostate cancer cells to PI3K-AKT-mTOR-targeted therapies being explored in the clinic, as well as standard treatment approaches such as androgen-deprivation therapy (ADT). However, the full extent of the PI3K-AKT-mTOR signaling network during prostate tumorigenesis, invasive progression and disease recurrence remains to be determined. In this review, we outline the emerging diversity of the genetic alterations that lead to activated PI3K-AKT-mTOR signaling in prostate cancer, and discuss new mechanistic insights into the interplay between the PI3K-AKT-mTOR pathway and several key interacting oncogenic signaling cascades that can cooperate to facilitate prostate cancer growth and drug-resistance, specifically the androgen receptor (AR), mitogen-activated protein kinase (MAPK), and WNT signaling cascades. Ultimately, deepening our understanding of the broader PI3K-AKT-mTOR signaling network is crucial to aid patient stratification for PI3K-AKT-mTOR pathway-directed therapies, and to discover new therapeutic approaches for prostate cancer that improve patient outcome.

Keywords: AKT; AR; castration-resistant prostate cancer (CRPC); MAPK; mTOR; PI3K; prostate cancer; therapeutic resistance; WNT

1. Introduction

Prostate cancer is the second leading cause of cancer-related deaths in men worldwide, despite extensive efforts to raise awareness and significant advancements in detection, screening, and treatment approaches [1–3]. Although patients with localized prostate cancer generally have a good prognosis, the 5-year relative survival rate is significantly reduced for patients that present with metastatic prostate cancer at diagnosis [4]. ADT and/or radiotherapy remains the mainstay treatment for patients that relapse post-surgery. ADT involves blocking the production of androgen in the testes via the hypothalamus-pituitary-gonadal axis with luteinizing hormone releasing hormone (LHRH) agonists (e.g., Leuprolide) or antagonists (e.g., Degorelix). Although prostate tumors respond initially to ADT, the emergence of androgen-independent, castration-resistant prostate cancer (CRPC) invariably occurs and the outcome is poor [5–8]. Treatment options for CRPC and patients with metastatic disease at diagnosis include chemotherapy, radium-223, second generation anti-androgens (e.g., the Cytochrome P450 17A1 (CYP17A1) inhibitor abiraterone acetate that prevents androgen biosynthesis,
or enzalutamide that targets AR directly), and clinical trials [5,6,8–10]. However, CRPC remains incurable and new biomarkers and treatments for prostate cancer and CRPC are in high demand.

PI3K-AKT-mTOR signaling is elevated in a high proportion of prostate cancer patients, and CRPC is associated with increased activation of the PI3K-AKT-mTOR pathway [11–13]. Accordingly, PI3K-AKT-mTOR pathway inhibitors are currently being explored as therapeutic agents against hormone-sensitive prostate cancer and CRPC [11–17]. PI3Ks are a large family of lipid kinase enzymes divided into three classes termed Class I (subdivided into Class IA and IB), Class II, and Class III, reflecting substrate specificity and subunit organization [18–20]. Class IA PI3Ks are heterodimers containing a catalytic subunit (p110α, p110β, or p110δ, encoded by PIK3CA, PIK3CB and PIK3CD respectively) and a regulatory subunit (p85α/p55α/p50α, p85β or p55γ, encoded by PIK3R1, PIK3R2 and PIK3R3 respectively) that controls protein localization, receptor binding, and activation [19–21]. Class IA isoforms are ubiquitously expressed, except for p110δ and p55γ that are primarily expressed in the hematopoietic/central nervous systems and testes [19–22]. Receptor tyrosine kinases (RTKs) can activate p110α, p110β, and p110δ catalytic isoforms, whereas the p110β isoform can be additionally activated by G protein-coupled receptors (GPCRs) [19–22] (Figure 1). The small GTPase RAS can also directly activate p110α and p110δ, while Rho-GTPases (e.g., RAC) are reported to activate p110β [20]. Once activated, Class IA PI3Ks initiate a wave of downstream signaling events by synthesizing the lipid secondary messenger phosphatidylinositol 3, 4, 5 trisphosphate (PIP3) from phosphatidylinositol 4,5 bisphosphate (PIP2) to mediate cell growth, proliferation, autophagy, and apoptosis [19,21]. The tumor suppressor, phosphatase and tensin homolog deleted on chromosome 10 (PTEN), negatively regulates PI3K-AKT-mTOR signaling by converting PIP3 back to PIP2 [23] (Figure 1).

Figure 1. PI3K-AKT-mTOR signaling interaction with the AR, MAPK, and WNT pathways. Image displays a model of PI3K-AKT-mTOR signaling via Class IA PI3Ks, and crosstalk with AR, RAS/MAPK, and WNT signaling cascades. 4EBP1, eukaryotic initiation factor 4E binding protein 1; AMP, adenosine...
monophosphate; AMPK, 5′ AMP-activated protein kinase; APC, adenomatous polyposis coli; ARE, androgen responsive element; AXIN, axis inhibition protein; BAD, Bel-2-associated death promoter; c-JUN, transcription factor AP–1; CaMKKa, Ca(2+)/calmodulin-dependent protein kinase kinase β; CK1, casein kinase 1; DEPTOR, DEP domain-containing mTOR-interacting protein; DHT, dihydrotestosterone; DVL, dishevelled; EIF4E, eukaryotic translation initiation factor 4E; ERBB2, Erb-B2 receptor tyrosine kinase 2, that encodes human epidermal growth factor 2/3 (HER2/3); ERG1, ETS-related gene 1; ERK, mitogen-activated protein kinase 1/3; EZH2, enhancer of zeste homolog 2; FKBPs, FK506 binding protein 5; FOXO, forkhead box protein O; FZD, frizzled family receptor; GDP, guanosine diphosphate; GPCR, G-protein coupled receptor; GSK3β, glycogen synthase kinase 3 beta; GTP, guanosine triphosphate; HSP90, heat-shock protein 90; IRS, insulin receptor substrate; KLK3, kallikrein related peptidase 3 (encoding prostate specific antigen, PSA); LKB1, liver kinase B1; LRPS/6, low-density lipoprotein receptor-related proteins 5 and 6; LEF, lymphoid enhancer binding factor 1; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2 homolog; MEK, mitogen-activated protein kinase kinase; mLST8, mTOR associated protein LST8 homolog; mSin1, mitogen-activated protein kinase associated protein 1 (MAPKAP1); mTOR, mammalian target of rapamycin; mTORC1/2, mTOR complex 1/2; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; P, phosphorylation event; PDK1, phosphoinositide dependent kinase 1; PHPPD, PH domain leucine-rich repeat protein phosphatase; PKCα, protein kinase C alpha; PR2A, protein phosphatase 2A; PRAS40, proline-rich AKT substrate of 40 kDa; PROTOR1, protein observed with Rictor-1; PROTOR2, protein observed with Rictor-2; RAF, rapidly accelerated fibrosarcoma; RAG, recombination activating genes; RAPTOR, regulatory-associated protein of mTOR; RHEB, Ras homolog enriched in brain; RICTOR, rapamycin-insensitive companion of mTOR; RPS6, ribosomal protein S6; RSK, 90 kDa ribosomal S6 kinase; RTK, receptor tyrosine kinase; SGK1, serum/glucocorticoid-regulated kinase 1; SLC43A1, solute carrier family 43 member 1 (encoding t-type amino acid transporter 3, LAT3); T, testosterone; TBC1D7, Tre2-Bub2-Cdc16 domain family member 7; TCF, T cell factor; TEL2, telomere length regulation protein (or telomere maintenance 2, Telo2); TSC1, Tuberous sclerosis complex 1; TSC2, tuberous sclerosis complex 2; TTI1, TEL2 interacting protein 1; ULK1, Unc-51 like autophagy activating kinase 1; WNT, WNT ligand. Figure based on previous work [12,14,19–22,24,25].

Elevated PIP3 levels lead to the activation of multiple kinases, including PDK1, which phosphorylates downstream targets such as AKT at residue Thr308 [19,21,26–28]. Activated AKT phosphorylates numerous substrates to regulate vital cellular processes, including FOXOs, GSK3β, NF-κB, and TSC2 [19,21,26–28]. For instance, TSC2 phosphorylation by AKT inactivates RHEB, which potentiates mTORC1 signaling and results in the inhibition of autophagy and increases cell growth, protein translation and ribosomal biogenesis via the subsequent phosphorylation of mTORC1 substrates such as ULK1, S6K, and 4EBP1 [27,29]. Phospho-S6K can also phosphorylate RICTOR to regulate mTORC2 signaling [30]. mTORC2 phosphorylates multiple downstream targets to mediate cell survival, cell cycle progression, and actin remodeling. These include AKT at residue Ser473, which leads to AKT hyperactivation, serum/glucocorticoid-regulated kinase 1 (SGK1) and protein kinase Ca (PKCa) [31,32].

In addition to mediating PI3K-dependent signaling, AKT, PTEN and mTORC1/2 have also been shown to play a role in PI3K-independent signaling events (reviewed in [23,33–36]), and the PI3K-AKT-mTOR cascade interacts with multiple cooperative signal transduction cascades via a series of partially understood interactions and feedback loops to promote tumor growth (including MAPK, AR and WNT signaling, Figure 1). Hence, establishing the scope of this complex signaling program is fundamental for the identification of new and effective biomarkers and therapeutic approaches that will benefit patients with prostate cancer.

2. Genetic Aberrations in the PI3K-AKT-mTOR Pathway in Prostate Cancer Are Diverse

Augmented phosphorylation/activation of key PI3K-AKT-mTOR pathway components (e.g., p-AKT and p-mTOR) has been shown to correlate with prostate cancer progression in the clinic [37–41].
Furthermore, genomic and transcriptomic profiling has revealed that genetic alterations and deregulated gene expression of PI3K pathway components are common in patients with prostate cancer, occurring in as many as 42% of primary and 100% of metastatic prostate cancer samples [42–46]. Deregulation of the PI3K-AKT-mTOR pathway reflects a variety of genetic alterations, primarily PTEN loss-of-function [42–46]. To improve our understanding of the frequency and diversity of PI3K-AKT-mTOR pathway genetic aberrations in prostate cancer, we used the cBioPortal platform to survey three publicly available prostate cancer genomic datasets with primary and/or metastatic patient samples for a panel of 68 genes that encode key PI3K cascade components/effectors [47,48]. OncoPrints displaying the percentage frequency of each type of genetic aberration assessed within each dataset (i.e., gene mutation, amplification and deep deletion) highlight that PI3K-AKT-mTOR pathway genetic alterations are commonplace in primary and metastatic prostate cancer, and illustrate that the wide range of genetic events observed have a tendency to co-occur (Figures S1–S3 and Tables S1–S3, summarized in Table 1).

Table 1. Frequency of common genetic alterations in PI3K-AKT-mTOR pathway genes in prostate cancer.

| Common Types of Genetic Alterations in PI3K-AKT-mTOR Pathway Genes | Frequency in Prostate Cancer ¹ |
|---------------------------------------------------------------|-----------------------------|
| PTEN deletion/mutation                                       | 16.4–32.0%                  |
| DEPTOR amplification                                         | 5.1–21.4%                   |
| SGK mutation/amplification                                   | 5.6–20.5% (SGK3)            |
| FOXO deletion                                                | 0.0–15.2% (FOXO1)           |
| MAP3K7 deletion                                              | 5.9–14.8%                   |
| RAGD deletion                                                | 6.5–14.4%                   |
| PIK3CA mutation/amplification                                | 5.5–11.5%                   |
| PIK3C2B mutation/amplification                               | 1.4–11.5%                   |
| PDPK1 amplification                                          | 0–8.1%                      |

¹ Data sourced from the Memorial Sloan Kettering Cancer Centre/Dana-Farber Cancer Institute (MSKCC/DFCI) (n = 1013) [45] and The Cancer Genome Atlas (TCGA), Firehose Legacy (n = 492) prostate adenocarcinoma datasets, and the metastatic prostate adenocarcinoma Stand Up To Cancer & Prostate Cancer Foundation International Dream Team (SU2C-PCF IDT) dataset (n = 444) [46] using cBioPortal [47,48] (Tables S1–S3). Only samples with mutation and copy number alteration (CNA) data were analyzed. The percentage frequency range for each genetic alteration listed reflects the entire patient population across all the three datasets, irrespective of the disease stage or subtype.

Common genetic alterations within the three prostate cancer datasets analyzed were observed in PTEN, DEPTOR, SGK3, FOXO1/3, MAP3K7, RAGD, SESN1, PIK3CA, PIK3C2B, and PDPK1 (Table 1). In addition, a vast range of less frequent aberrations were also detected, including genes encoding AMPK subunits (e.g., amplification of PRKAB1 and PRKAB2) and AMPK regulators (e.g., CAMKK2 and LKB1 deletion) (Figures S1–S3, Tables S1–S3), as described below.

2.1. PI3K Gain of Function

2.1.1. Class IA PI3Ks

Gain-of-function mutations in PIK3CA (encoding p110α) that activate the PI3K cascade are highly prevalent in a number of malignancies, including up to 40% of breast cancer patients [49] and as many as 53% of endometrial cancer patients [50]. In the prostate cancer datasets analyzed, PIK3CA mutation and high-level gene amplification occur in up to 4% and 9% of cases respectively (Tables S1–S3), although high-level amplification has been observed previously in as many as 29% of cases [13]. Our recent work identified that PIK3CA genetic alterations significantly correlate with poor prostate cancer prognosis, and that Pik3ca oncogenic mutation at a clinically relevant hotspot (H1047R) in mouse prostate epithelium can cause locally invasive prostate adenocarcinoma, demonstrating Pik3ca activation is a genetic driver of prostate cancer in vivo [13]. Although less common, PIK3CB mutation and amplification have also been detected in clinical prostate tumor specimens (0.6–1.8% and
1.8–3.1% respectively, Tables S1–S3), and activation of p110β (encoded by PIK3CB) predisposes prostate intra-epithelial neoplasia in mice [51]. Previous work has shown that p110α isomeric-specific PI3K inhibitors can suppress Pik3ca mutant prostate cancer, whereas a p110ββ inhibitor, or combined p110αβ blockade improves therapeutic outcome in Pten-deficient (p110β-dependent) prostate cancers [13,52,53]. Consequently, these findings have identified that selected p110 isoform-specific inhibitors may prove to hold efficacy against PIK3CA mutant and PTEN-deleted prostate cancer in the clinic.

Unlike the ubiquitous p110α and p110β PI3K catalytic isoforms, p110δ is predominantly expressed in cells of hematopoietic lineage and sensory neurons [54–56], and p110δ isoform-specific inhibitors are currently being explored in the clinic for B-cell malignancies and some autoimmune diseases [57]. However, several epithelial malignancies have also been shown to express p110δ [58], and 3% of patients with head and neck, germ cell, or colorectal cancer are reported to carry a PIK3CD mutation [59]. In patients with prostate cancer, PIK3CD mutation and amplification are infrequent events (≤1.1%, Tables S1–S3). However, a PIK3CD splice variant missing exon 20 (PIK3CD-S) has been identified in African American prostate cancer patients that can promote proliferation and AKT-mTOR signaling [60], and several CRPC cell lines have been shown to express p110δ at high levels, comparable to that detected in leukocytes [58]. In this study, inactivation of p110δ in p110δ-high CRPC cells suppressed PI3K-AKT signaling and inhibited cell proliferation, suggesting p110δ inhibitors may prove to hold therapeutic efficacy against p110δ-high prostate cancer [58].

The p85 regulatory subunit of PI3K is often present in a monomeric free form, and at a higher ratio relative to the p110 catalytic subunit, which suppresses p110 activity in the absence of stimuli [20,61,62]. Both free p85 monomers and p85–p110 heterodimers have been shown to bind to insulin receptor substrate (IRS), a cytoplasmic adaptor protein for the RTK insulin growth factor 1 (IGF-1) receptor, in addition to directly binding with activated RTKs [20,61]. Nonetheless PI3K-AKT-mTOR signaling activation is considered to require p85–p110 heterodimerization [20,61]. Interestingly, constitutive heterozygous deletion of PIK3R1 (that encodes p85α and splice variants p55α/p50α) has been shown to lower blood glucose, enhance insulin sensitivity, potentiate insulin–stimulated glucose transport in skeletal muscle and adipocytes, and can stimulate insulin-dependent AKT phosphorylation in mouse liver [63,64]. Furthermore, liver-specific deletion of Pik3r1 in mice is reported to not only enhance insulin and growth factor signaling, but causes development of aggressive hepatocellular carcinomas with pulmonory metastases associated with AKT activation and decreased PTEN expression [65]. PIK3R1 shRNA-mediated knockdown in human breast cancer cell lines can also augment AKT signaling and anchorage-independent growth, illustrating a tumor suppressive role for p85α in breast cancer [66]. While p85α is generally viewed as a tumor suppressor, evidence in the literature also points toward an oncogenic role, similarly to p85β and p55γ [67–71].

In prostate cancer, PIK3R1 is rarely mutated (0.4–1.6% of cases) yet deep deletions occur in 1–6% of patients (Tables S1–S3), which could potentially promote PI3K-AKT-mTOR signaling. Genetic alterations in PIK3R2 (percentage incidence: mutation < 1.1%, amplification < 2.9%, deletion < 0.23%, Tables S1–S3) and PIK3R3 (percentage incidence: mutation < 0.7%, amplification < 0.5%, deletion < 1%, Tables S1–S3) are also infrequent, yet the functional significance of these events remains unclear. Interestingly, down-regulation of PIK3R1 in prostate cancer has been linked to reciprocal negative feedback between the AR and PI3K signaling cascades [72], and PIK3R3 upregulation has been linked to prostate hyperplasia [73]. Furthermore, PIK3R2 upregulation in prostate cancer specimens has recently been shown to inversely correlate with miR-126 expression [74]. Song and colleagues identified PIK3R2 as a direct target of miR-126 in prostate cancer cell lines, and reported that enforced miR-126 expression in prostate cancer cell lines reduces PIK3R2 mRNA expression and suppresses cell proliferation, migration, and invasion [74].

2.1.2. Class IB PI3Ks

The smaller Class IB PI3K family is comprised of the catalytic subunit p110δ and two regulatory subunits, p101 and p87 (also known as p84), which are encoded by PIK3CG, PIK3R5, and PIK3R6.
respectively. Like Class IA, Class IB PI3Ks generate PIP3 from PIP2 to stimulate downstream effectors [19]. Class IB PI3Ks transmit Gβγ-GPCR and RAS signals to coordinate immune, inflammatory and allergic responses, predominantly within hematopoietic cells [18–20,22]. However, Brazzatti and colleagues have shown that knockdown of p110γ or p101 in 4t1.2 and MDA-MB-231 triple-negative breast cancer cell lines reduces migration in vitro and metastatic potential in xenograft mouse models, whereas p87/p84 knockdown had the opposite effect [75]. PIK3CG mutation and amplification are frequent in multiple malignancies, including 9–11% of melanomas and uterine, stomach and squamous cell lung cancers, while genetic alterations in PIK3R5 and PIK3R6 are prevalent in uterine cancer and melanoma, occurring in 4–8% of cases [50,76–79]. In prostate cancer, Class IB PI3K genetic aberrations are less common, and include PIK3CG mutation and amplification (1.4–1.8% and 0.6–3.6% incidence respectively) as well as PIK3R5 and PIK3R6 deep deletions (0–3.3% incidence) that are indicative of a homozygous deletion (Tables S1–S3).

2.1.3. Class II PI3Ks

In comparison to Class I PI3Ks, the Class II family of PI3Ks (PI3KC2α, β and γ, encoded by PIK3C2A, PIK3C2B, and PIK3C2G respectively) is less well-characterized. Class II PI3Ks are generally considered to catalyze the production of lipid secondary messengers phosphatidylinositol 3-phosphate (PtdIns3P or PI(3)P) and phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) to mediate cell migration, channel regulation, endocytosis, and exocytosis [18,80]. The frequency of PIK3C2A, PIK3C2B and PIK3C2G mutation is generally low (0.2–1.4% incidence, Tables S1–S3), however PIK3C2B amplification has been observed in as many as 10% of cases (Table S3). Although the role of PIK3C2B amplification in prostate cancer is not clear, a recent study identified that PI3KC2β is highly expressed in PTEN-negative PC3 and LNCaP prostate cell lines compared to PTEN-positive DU145 prostate cancer cells (PTEN+/−), and PNT2 immortalized “normal” prostate epithelial cells (PTEN+/+) [81]. This study also reported that PI3KC2β regulates MAPK signaling to mediate prostate cancer cell invasion, thus the PI3KC2β-MEK-ERK signaling axis may present a novel therapeutic target for invasive prostate cancer [81].

2.1.4. Class III PI3Ks

The Class III PI3K subfamily is comprised of the catalytic subunit vacuolar protein sorting 34 (VPS34) encoded by PIK3C3, and the regulatory subunit vacuolar protein sorting 15 (VPS15, or p150) encoded by PIK3R4. VPS34 catalyzes the phosphorylation of phosphatidylinositol (PI) to produce PI(3)P, which plays a central role in the regulation of intracellular trafficking [82]. To regulate the fusion and maturation of endosomes, VPS34 binds to VPS15 and Beclin-1 to form either VPS34 Complex I or VPS34 Complex II that differ by binding to Autophagy Related 14 (ATG14) or UV radiation resistance associated protein (UVRAG) respectively [83]. The Class III PI3K family has also been shown to mediate autophagy, endosome–lysosome maturation, membrane trafficking, and AMPK-dependent insulin sensitivity [82,84–89].

PIK3C3 mutations are most frequently observed in uterine and gastric cancer patients (7% and 3.5% respectively), and PIK3R4 gene mutation or amplification occur in up to 10% of squamous cell lung cancer and uterine cancer patients [50,76,77]. Although PIK3C3/PIK3R4 mutation and PIK3C3 gene amplification are infrequent events in prostate cancer (<1% of cases), PIK3R4 high-level gene amplification is observed in up to 6.5% of cases and could potentially facilitate prostate cancer growth (Tables S1–S3).

Taken together, these data highlight the emerging diversity of genetic alterations within the PI3K family in prostate cancer, and emphasize the need for future work to gain further insight into the functional importance of these different genetic alterations during prostate cancer formation, progression, and recurrence. This is particularly important, as determining their non-redundant roles may present novel therapeutic targets and could aid patient stratification for future clinical trials.
2.2. Loss of Function of Phosphoinositide Phosphatases

Phosphoinositide phosphatases are a family of enzymes that dephosphorylate phosphoinositides to diminish phosphoinositide signals and regulate cellular functions [90]. The PI3K-AKT-mTOR pathway is regulated by multiple phosphoinositide phosphatases, including the tumor suppressor PTEN that dephosphorylates PIP3 into PIP2 to reduce PI3K-AKT-mTOR pathway activity (Figure 1). Genetic alterations in phosphoinositide phosphatases are strongly associated with human malignancies, and PTEN is one of the most frequently deleted genes in prostate cancer [91–95]. Here we review the frequency of genetic alterations in prostate cancer for genes encoding key phosphoinositide phosphatases known to regulate the PI3K-AKT-mTOR cascade.

2.2.1. Loss or Inactivation of PTEN

PTEN is a lipid/protein phosphatase that has been shown to negatively regulate the PI3K-AKT-mTOR pathway by dephosphorylating phosphatidylinositol (3,4,5)-trisphosphates (PIP3) back to phosphatidylinositol 4,5-bisphosphates (PIP2) (Figure 1) [23,96,97]. PTEN genetic alterations, primarily homozygous deletion, are common in advanced prostate cancer and significantly correlate with poor outcome and elevated PI3K-AKT-mTOR signaling [13,14,37,39,98,99]. The functional consequence of PTEN loss has been studied in vivo using a number of genetically engineered mice, which have demonstrated PTEN loss is a genetic driver of invasive prostate cancer [24,100–104]. Homozygous Pten deletion within the murine prostate epithelium leads to aggressive, locally invasive prostate carcinoma that has an inherent ability to acquire castration-resistant disease [13,24,100–102,105]. However, metastatic disease is rare in these models, possibly owing to the primary tumor reaching ethical limits before disseminated cells can colonize distant sites, differences in genetic background, and/or PTEN loss-induced p21/p53-dependent senescence [102–104,106,107].

In primary prostate adenocarcinoma, PTEN mutation and deep deletion occur in 2% and 18% of cases respectively (Table S1), and the frequency appears to increase in metastatic disease (6% and 26% respectively, Table S3). Although the majority of PTEN mutations identified in prostate cancer are truncating mutations, missense mutations are also observed, which could differentially impact PTEN lipid and/or protein phosphatase function [108]. Thus, determining how each PTEN genetic alteration impacts PTEN function may inform clinical trial design.

PTEN heterozygous deletion and epigenetic silencing can also deplete PTEN expression/function [92,98,106,109]. Importantly, mono-allelic deletion of PTEN has been reported in up to 68% of prostate cancer surgical specimens and PTEN immunohistochemistry (IHC) and/or fluorescent in situ hybridization analysis has revealed PTEN loss may occur in as many as 60% of advanced/CRPC cases [92]. A subset of patients with prostate cancer have also been found to harbor intratumoral heterogeneous PTEN loss [92], which could have significant implications for therapeutic strategies.

2.2.2. Deregulation of Phosphoinositide Phosphatase Enzymes (other than PTEN)

In addition to PTEN, several other phosphatidylinositol phosphate phosphatase enzymes are also deregulated in human cancers that have the potential to facilitate malignant growth [90,91,110]. These phosphatases include; (a) proline-rich inositol polyphosphate 5-phosphatase (PIPP) encoded by polyphosphate-5-phosphatase J (INPP5J), (b) Src homology 2 (SH2) domain-containing inositol 5'-phosphatase 1 (SHIP1) encoded by inositol polyphosphate-5-phosphatase D (INPP5D), (c) Src homology 2 (SH2) domain-containing inositol 5'-phosphatase 2 (SHIP2) encoded by inositol polyphosphate phosphatase like 1 (INPPL1), and (d) inositol polyphosphate 4-phosphatase type II (INPP4B) encoded by INPP4B. While PTEN converts PIP3 to PIP2, PIPP and SHIP1/2 dephosphorylate PIP3 to phosphatidylinositol (3,4)-bisphosphate PI(3,4)P2, which is further hydrolyzed by INPP4B to form PI(3)P [90,111]. INPP5D deep deletion is observed in as many as 3.8% of patients with prostate cancer whereas INPPL1 and INPP4B are amplified in up to 2.9% of cases (Tables S1–S3).
INPP5D/[INPPPL]/[INPP5J]/INPP4B mutation, INPP5J amplification and INPPL1/[INPP4B]/INPP5J deep deletion events are rare (≤1.2%, Tables S1–S3). Relative to PTEN, the frequency of genetic alterations in these phosphoinositide phosphatases is much lower, however they are gaining increasing attention in the literature [111]. Interestingly, PIPP deletion is reported to increase tumor growth in the mouse mammary tumor virus-polyoma middle tumor-antigen (MMTV-PyMT) breast cancer model, and is accompanied with elevated proliferation, plasma membrane PIP3 levels, and AKT activation [110]. However, PIPP deletion also significantly reduced the incidence of lung metastasis in this setting, suggesting PIPP mediates a critical metastatic process [110,112]. Furthermore, INPP4B can compensate for PTEN loss by acting as a “back-up” phosphatase, and is regarded as a tumor suppressor in several epithelial tissues including the prostate, breast, ovary, and thyroid [112–116]. Notably, Inpp4B loss and Pten heterozygous deletion can cooperate in mice to facilitate metastatic thyroid cancer by increasing PIP3 levels and AKT signaling relative to single mutants [115], and enforced INPP4B overexpression in PC3 (PTEN−/−) and DU145 (PTEN−/−) prostate cancer cells can suppress prostate cancer cell migration and invasion, both in vitro and in vivo [117]. Immunostaining to detect INPP4B in prostate carcinoma clinical samples has also identified INPP4B loss as an independent prognostic marker, correlating with reduced biochemical (PSA) relapse-free survival [118]. In contrast, SHIP2 is reported to play an oncogenic role. Unlike PTEN that catalyzes PIP3 into PIP2, SHIP2 converts PIP3 into PI(3,4)P2 to further potentiate AKT activity [119,120]. Moreover, increased SHIP2 expression directly correlates with poor survival in patients with colorectal cancer [120]. Consequently, genetic aberrations in phosphoinositide phosphatase enzymes could prove to differentially influence therapeutic responses to PI3K pathway-directed therapies.

2.3. AKT Gain of Function

AKT isoforms 1, 2, and 3 (encoded by AKT1, AKT2, and AKT3 respectively) form a subfamily of serine/threonine protein kinases that possess both overlapping and distinct cellular functions to regulate a variety of cellular processes during normal tissue homeostasis and cell transformation [121,122]. PI3K activity elevates PIP3 levels to recruit AKT to the plasma membrane where it is activated (Figure 1). AKT is activated by multiple kinases, including PDK1 and mTORC2 that phosphorylate AKT at residues Thr308 and Ser473 respectively, triggering a wave of phosphorylation through multiple downstream targets that stimulate cell survival, proliferation, metabolism and differentiation to promote tumor growth [19,20,32,123,124]. AKT downstream targets include PRAS40 (a component of mTORC1), BAD, FOXOs, and MDM2 (reviewed in [31]). AKT signaling is negatively regulated by several protein phosphatases that dephosphorylate and inactivate AKT, including protein phosphatase 2 (PP2A), and phosphoinositide phosphatase enzymes could prove to differentially influence therapeutic responses to PI3K pathway-directed therapies.

2.3.1. AKT Mutation and Amplification

AKT genetic aberrations that increase AKT activity have been detected in multiple malignancies and are especially common in breast cancer, where AKT3 amplification and AKT1 E17K oncogenic mutation have been reported in up to 24% and 1–8% of cases respectively [127–129]. AKT1, AKT2, and AKT3 activating mutations are rare in prostate cancer (≤0.9%, predominantly in AKT1 at E17K), whereas AKT1, AKT2, and AKT3 high-level gene amplification that can increase AKT activity is more common, particularly in advanced disease (up to 4.5%, 2%, and 4.7% incidence respectively, Tables S1–S3). Moreover, AKT activation in prostate cancer has been shown to positively correlate with Gleason score and invasive progression [37,130], and over-expression of myristoylated AKT (which causes constitutive AKT activation) causes prostate neoplasia in mice [131]. In support of an oncogenic role in prostate cancer and therapeutic resistance, conditional activation of AKT in either the LNCaP human prostate cancer cells or a transgenic mouse results in increased cell proliferation and inhibits cell...
death to promote tumor growth and castration-resistance in vivo [132]. Chen and colleagues have also demonstrated a requirement for AKT in PTEN-deficient prostate cancer, as Akt1 haplodeficiency was found to suppress high-grade prostate intraepithelial neoplasia development within Pten heterozygous mice [133]. AKT inhibitors are being widely explored in the clinic to treat prostate cancer and have shown promise in PTEN-deficient patients [16,134].

2.3.2. Genetic Alteration of AKT Regulators

A number of genetic alterations in genes that encode AKT regulators have been linked to prostate cancer, including kinases (e.g., PDK1), binding proteins (e.g., FKBP5), and phosphatases (e.g., PHLPP1, PHLPP2, and PP2A) [42–46]. PDK1 (encoded by PDPK1) is recruited to the membrane by PIP3 to phosphorylate and activate multiple targets, including AKT at residue T308 (Figure 1). PDPK1 amplification and PDK1 over-expression are observed in several human cancers, including breast cancer [135]. In prostate cancer, PDK1 mutations are rare (≤0.2%), yet PDK1 amplification occurs in up to 8.1% of patients (Tables S1–S3). Interestingly, PDK1 RNAi-mediated knockdown does not impair Pten-deleted prostate cancer growth in mice, possibly reflecting mTORC2-mediated activation of AKT, and/or compensatory augmentation of the MAPK cascade [136]. These findings suggest that PDK1 inhibitors are not likely to be efficacious against PTEN-deficient prostate cancer in the clinic as a single agent.

FKBP5 (also known as FKBP51) is an AR target gene that plays a key role in mediating the cellular distribution of steroid hormone receptors and has been shown to negatively regulate AKT signaling by stabilizing PHLPP1/2 (Figure 1) [11,24,137]. During androgen/AR-directed therapy, FKBP5-PHLPP1/2-AKT signaling forms a negative feedback loop between the AR and PI3K-AKT-mTOR pathways to facilitate ADT resistance [11,24,137], discussed in Section 3.2. Mutation and deep deletion of FKBP5 are fairly infrequent in prostate cancer (≤1.22%, Tables S1–S3), however FKBP5 down-regulation has been linked to CRPC and increased AKT signaling [11].

PHLPP1 and PHLPP2 (encoded by PHLPP1 and PHLPP2) are protein phosphatases that dephosphorylate and inactivate AKT. PHLPP1 and PHLPP2 deep deletion occurs in up to 3.9% and 6.5% of patients with prostate cancer respectively (Tables S1–S3), which could potentially sustain AKT-signaling. Interestingly, Chen and colleagues reported a strong tendency for Pten, PHLPP1, PHLPP2, and TP53 co-deletion in metastatic prostate cancer and that low PHLPP1 expression correlates with reduced patient survival and relapse after surgery [138]. Additionally, the tumor suppressive function of PHLPP1 has been demonstrated in vivo, as Phlpp1 loss causes prostate neoplasia in mice and promotes invasive carcinoma progression in Pten−/− transgenic mice [138]. In contrast, Phlpp2 loss impairs Pten/p53-deleted prostate tumor growth in mice [139], indicating PHLPP1 and PHLPP2 mediate differential AKT-independent functions. Indeed, PHLPP2 can dephosphorylate MYC at residue Thr58 to prevent MYC degradation and promote tumor progression [139]. Consequently, in PHLPP2-positive MYC-driven advanced prostate cancer, it has been suggested that PHLPP2 may present a valuable therapeutic target [139].

In addition, genetic alterations in PPP2CA (protein phosphatase 2 catalytic subunit alpha) that encodes the negative AKT regulator PP2A have also been observed in prostate cancer [42–46], and PP2A loss has been linked to prostate cancer progression and metastatic potential in the clinic [140]. PPP2CA mutation and deep deletion events occur in 0.4–1.4% of patients with prostate cancer (Tables S1–S3), further highlighting the diversity of genetic aberrations in AKT regulators that could promote oncogenic PI3K signaling.

2.4. SGK Deregulation

The serum/glucocorticoid-regulated kinase isoforms SGK1, SGK2, and SGK3 belong to a subgroup of the AGC (cAMP-dependent, cGMP-dependent, and protein kinase C) family of protein kinases that play a role in multiple cellular processes including cell growth, proliferation, metabolism, intracellular trafficking and survival [141–143]. SGK1 and 3 are considered to be ubiquitously expressed, while
SGK2 expression is prominent in the liver, kidney, pancreas, and brain [144]. SGKs share structural similarities, upstream regulators, substrates and functions with the AKT isoforms (reviewed in [142]). For instance, all SGKs are phosphorylated and activated by PDK1, and SGK1 is a downstream target of mTORC2 [26,143,145–148] (Figure 1). SGKs are also activated by PI3K/PDK1-independent mechanisms, for example SGK1 is regulated by big mitogen-activated protein kinase-1 (BMK-1) and p38 mitogen-activated protein kinase in response to epidermal growth factor (EGF) and interleukin-6 (IL6) respectively [149,150]. Although the role of SGKs during prostate cancer is currently unclear, SGK1 over-expression has been shown to facilitate CRPC transition in a prostate cancer xenograft model, indicating that SGK1 can promote ADT-resistance [151]. Furthermore, the SGK1 inhibitor GSK650394 has been shown to induce autophagy and apoptosis in PC3, LNCaP, DU145, and CWR22RV1 prostate cancer cells in vitro [152]. Interestingly, SGK1 and SGK3 have also been linked to PI3K/AKT-targeted therapy resistance in breast cancer [145,148]. Gasser and colleagues have also shown that INPP4B over-expression leads to enhanced SGK3 activation in ZR-75-1 breast cancer cells, triggering a switch from AKT- to SGK-dependent signaling downstream of PDK1 [153].

Mutation of the SGK isoforms is a rare event in human cancers, however gene amplification is commonly detected [154]. In keeping with this, SGK1, SGK2, and SGK3 are rarely mutated in prostate cancer (≤0.41%), whereas amplification occurs in up to 2.5%, 2.0%, and 20.3% of cases respectively (Tables S1–S3). Of note, the frequency of SGK3 gene amplification is particularly high in the SUC2/PCF IDT metastatic prostate adenocarcinoma dataset (Table S3), underlining the need for future studies to establish how SGKs contribute to prostate cancer and metastatic progression.

2.5. Loss of FOXO Transcription Factors

The mammalian forkhead box O (FOXO) family consists of four transcription factors (FOXO1, 3, 4, and 6) that are highly similar in structure and function [155]. In response to insulin and growth factors, FOXOs modulate the transcription of several target genes to mediate key cellular processes including proliferation, apoptosis, autophagy, inflammation, metabolism and stress resistance, and they form an important regulatory circuit within the AKT and mTOR signaling cascades [156–158] (Figure 1). FOXOs are regulated by several kinases, including AKT and SGK isoforms, which phosphorylate and inactivate FOXO-mediated gene transcription by inhibiting FOXO DNA binding and triggering FOXO nuclear-to-cytoplasm translocation [157–159]. FOXOs are generally regarded as tumor suppressors, and are reported to inhibit mTORC1 via sestrins, however a number of oncogenic functions are emerging in the literature [156–158]. For instance, FOXO-mediated transcription of the mTORC2 component RICTOR in response to physiological stress is reported to promote mTORC2 signaling [156]. FOXOs also provide a reciprocal negative feedback loop between PI3K-AKT-mTOR pathway and AR signaling [12] (discussed in Section 3.2).

In prostate cancer, FOXO mutations are rare (<0.5% incidence), however FOXO1 and FOXO3 deep deletion is a frequent event, occurring in up to 15.2% and 13.4% of patients respectively (Tables S1–S3). FOXO3 lies within the 6q21 locus that is frequently lost in prostate cancer [160], and reduced FOXO3 (also FOXO3a) activity via peptide driven inhibition is reported to accelerate prostate cancer progression in the transgenic adenocarcinoma mouse prostate (TRAMP) neuroendocrine prostate cancer model [161]. FOXO1 has also been shown to bind and inhibit the transcriptional activity of E26 transformation-specific (ETS) transcription factor ERG, which is over-expressed in 50% of prostate cancers owing to TMPRSS2-ERG (transmembrane protease, serine 2: ERG fusion) gene rearrangements [162]. Furthermore, Foxo1 bi-allelic deletion and ERG overexpression can cooperate to cause prostate neoplasia in mice [162]. Together, these findings suggest FOXO1/3 act as tumor suppressors during prostate cancer.

FOXO4 gene amplification occurs in up to 8.8% of patients with metastatic prostate cancer (Table S3), however the functional importance of this genetic alteration remains to be clarified. Although FOXO4 down-regulation is reported to correlate with reduced prostate cancer metastasis-free survival,
conversely FOXO4 knockdown in LNCaP cells can increase metastatic potential [163]. Thus, future work addressing the role of FOXO4 during prostate cancer progression is warranted.

2.6. TSC1-TSC2-TBC1D7 Complex and RHEB Deregulation

To regulate mTORC1 signaling, TSC1, TSC2, and TBC1D7 form a complex to suppress RHEB GTPase, an upstream activator of mTORC1 [164] (Figure 1). Activated AKT directly phosphorylates TSC2 at multiple residues to inhibit the TSC1:TSC2 complex, activate RHEB GTPase, and subsequently stimulate mTORC1 signaling [165,166]. TSC2 is also regulated by MAPK, WNT, and energy signals through coordinated phosphorylation by ERK, GSK3, and AMPK respectively, thus limiting mTORC1 activation and cell growth in response to poor growth conditions, and illustrating TSC2 as a central node for PI3K-AKT-mTOR crosstalk with multiple signaling cascades [164,166–168].

TSC1 and TSC2 are frequently mutated/deleted in a variety of solid tumors, including lung (22%) and liver (16%) cancers, leading to deregulated PI3K-AKT-mTOR signaling [169,170]. In prostate cancer, the frequency of TSC1 and TBC1D7 mutation or deep deletion is low (≤0.8% incidence, Tables S1–S3), whereas TSC2 mutation and deep deletion are more frequent (1–1.8% and up to 4.2% of cases respectively, Tables S1–S3). Interestingly an inactivating splice variant of TSC2 unique to African American patients with prostate cancer has also recently been linked to aggressive prostate cancer and therapeutic resistance [60]. In mice, Tsc1 conditional deletion in murine prostate epithelium is reported to cause prostate neoplasia associated with elevated mTORC1 signaling [171], and combined Tsc2 and Pten heterozygosity has been shown to promote invasive prostate carcinoma relative to single mutants [172]. In lung cancer, TSC1 and TBC1D7 have been shown to function as oncoproteins [173], possibly reflecting mTORC1-independent functions such as TSC1-mediated activation of TGFβ-SMAD2/3 signaling [174]. Remarkably, up to 3%, 4%, and 7% of patients with prostate cancer also display TBC1D7, TSC1, and TSC2 high-level amplification respectively (Tables S1–S3), yet the functional consequence is currently unclear.

RHEB GTPase has also been shown to act as a proto-oncogene in prostate cancer and up to 4% of patients with prostate cancer carry RHEB gene amplification, however RHEB oncogenic mutations are rare (≤0.1% incidence, Tables S1–S3). RHEB GTPase is over expressed in several prostate cancer cell lines and transgenic mice over-expressing Rheb specifically within the prostate epithelium develop low-grade prostatic intraepithelial neoplasia lesions by 10 months of age, accompanied with increased mTORC1 activity [175]. Rheb over-expression can also cooperate with Pten haploinsufficiency to promote prostate tumorigenesis [175], indicating RHEB amplification is likely to be a genetic driver of prostate tumorigenesis in the clinic.

2.7. Amplification of mTORC1 and mTORC2 Complex Components

The mTORC1 and mTORC2 protein complexes are functionally and structurally distinct, originally distinguished by their sensitivity to the mTOR inhibitor rapamycin [176–178]. Both mTORC1 and mTORC2 complexes contain mTOR, MLST8 (also known as G-protein beta-subunit like, GβL), TEL2, TTI1, and the negative regulator DEPTOR [179,180]. RAPTOR and PRAS40 (encoded by AKT1S1) are additional members of mTORC1 complex, whereas RICTOR, mSin1, and PROTOR1/2 form the mTORC2 complex [180] (Figure 1). mTORC1 and mTORC2 are downstream effectors and regulators of PI3K/AKT signaling that mediate key cellular processes in response to growth factors and hormones [179,181–183]. mTORC1 is sensitive to rapamycin treatment and functions to regulate cell growth, autophagy, protein translation machinery, and cell-cycle progression by phosphorylating substrates such as ULK1, S6K and 4EBP1 [179,183–185]. The mTORC2 complex plays a critical role in PI3K/AKT signaling by increasing the activity of AKT, SGK1 and PKCa to regulate cell survival, metabolism and cytoskeletal dynamics [184] (Figure 1). mTORC2 is generally insensitive to rapamycin [179], however chronic exposure to the drug has been shown to impair mTORC2 assembly [185]. Crucially, mTORC1 and mTORC2 can also regulate each other via multiple
mechanisms, including AKT regulation of PRAS40 to block suppression of mTORC1 activity and S6K regulation of mSIN1 to modulate mTORC2 activity [186].

In general, the frequency of genetic alterations in mTORC1 and mTORC2 components is low in prostate cancer. Genomic profiling data have shown that mTOR mutation occurs in 0.6–1.6% of cases, and the frequency of mutation or deep deletion in the other components of mTORC1/2 is ≤1% (Tables S1–S3). However, DEPTOR gene amplification is comparatively frequent, occurring in 5.1–21.4% of cases, with the highest incidence observed in the SUC2/PCF-IDT metastatic prostate adenocarcinoma dataset (Tables S1–S3). In addition, DEPTOR amplification directly correlates with worse disease/progression-free survival in the TCGA Firehose Legacy prostate adenocarcinoma dataset (Figure S4), indicating DEPTOR amplification may provide a valuable predictive biomarker in the clinic. DEPTOR is an endogenous suppressor of mTOR kinase activity, yet DEPTOR upregulation can reduce S6K1 activation, thus relieving feedback inhibition from mTORC1 to PI3K and mTORC2 signaling that results in increased AKT activation [187]. Nevertheless, DEPTOR knockdown in colorectal cancer cells reduced cell proliferation and induced differentiation [188], raising the possibility that DEPTOR can promote tumorigenesis in other epithelial cancers. DEPTOR has also been shown to exert mTORC1/2-independent functions in the nucleus as a transcriptional regulator in multiple myeloma cells [189] and is a transcriptional target of WNT/β-catenin/MYC signaling in colorectal cancer cells [188], adding further complexity to PI3K-AKT-mTOR and WNT pathway crosstalk.

In addition to DEPTOR, a number of other genes encoding mTOR components were also distinctly amplified in the SUC2/PCF-IDT metastatic prostate cancer dataset (AKT1S1, 2.7%; MLST8, 7.7%; MAPKAP1, 4.5%; RPTOR, 7%; RICTOR, 5%; TEO2, 6.5%; TTI1, 2.5%, Table S3), which could potentially facilitate tumor progression. However, none of these genetic alterations correlate with disease/progression-free survival (determined by cBioPortal analysis of the TCGA Firehose Legacy prostate adenocarcinoma dataset, n = 492, data not shown) [47,48]. Significantly, bi-allelic deletion of Rictor in mouse prostate epithelium has revealed RICTOR is not required for normal tissue homeostasis, yet RICTOR loss can suppress Pten-deleted prostate tumorigenesis in mice [190]. These findings indicate that mTORC2 signaling can contribute to PTEN-deleted prostate cancer growth, and that mTORC2 inhibition may be efficacious in the clinic against prostate cancers with PTEN loss [190].

Intracellular amino acids can also activate mTORC1 signaling by stimulating vacuolar H+−ATPase (v-ATPase) to activate Ragulator, a guanine exchange factor that converts RAGA/B-GDP to RAGA/B-GTP, enabling formation of the active RAG complex where RAGA-GTP or RAGB-GTP form heterodimers with either RAGC-GDP or RAGD-GDP [36,191–195]. Similarly to RAGA/RAGB, RAGC/RAGD are functionally redundant and are 80–90% homologous [195]. When amino acids are sufficient, mTORC1 is recruited to the lysosome where it binds to the active RAG complex via RAPTOR, followed by its localization to RHEB that leads to mTORC1 activation [36,191,195] (Figure 1). Recent evidence also suggests that amino acids such as glutamine can activate mTORC1 in a RAG-complex independent manner, for example via the GTPase adenosine ribosylation factor 1 (ARF1) [196], highlighting the complex nature of mTORC1 regulation.

In prostate cancer, genetic alterations in RRAGA and RRAGC genes that encode RAGA and RAGC respectively are uncommon, however RRAGB (encoding RAGB) is amplified in up to 7.7% of cases and RRAGD (encoding RAGD) deep deletion occurs in 6.5–14.4% of cases (Tables S1–S3). Interestingly, RRAGD deep deletion in prostate adenocarcinoma strongly correlates with FOXO3 deletion (one-sided Fisher’s Exact test, p-value < 0.001; data sourced from the cBioPortal platform, TCGA Firehose Legacy prostate adenocarcinoma dataset, n = 492), however the functional consequence of RRAGD/FOXO3 co-deletion and RAGB amplification during prostate cancer growth and therapeutic resistance is currently unknown and merits further investigation.

2.8. Aberrant AMPK Signaling

The metabolic sensor AMPK functions to maintain an adenosine triphosphate (ATP) equilibrium, influencing cell growth, lipid and glucose metabolism, autophagy and cell polarity [197]. AMPK
is composed of a catalytic subunit ($\alpha_1/\alpha_2$, encoded by PRKAA1/PRKAA2), a $\beta$ structural subunit ($\beta_1/\beta_2$, encoded by PRKAB1/PRKAB2) and a regulatory $\gamma$ subunit ($\gamma_1/\gamma_2/\gamma_3$, encoded by PRKAG1/PRKAG2/PRKAG3) [198]. AMPK activation plays a tumor suppressive role by inhibiting mTORC1 through the phosphorylation of TSC2 and RAPTOR in response to energy stress [199] (Figure 1), and by negatively regulating lipogenesis [200–202]. AMPK can also play an oncogenic role during stress (including hypoxia, oxidative stress, and glucose deprivation) to activate AKT, yet the molecular mechanisms involved remain to be fully elucidated [200]. Mutation and deep deletion of the AMPK subunits are uncommon in human malignancies [203], including prostate cancer (<1.2% incidence, Tables S1–S3). Instead, gene amplification of the AMPK subunits is more common [43,45,204]. In prostate cancer, high-level amplification of PRKAB1, PRKAB2, PRKAG2, and PRKAG3 occurs in up to 6.3%, 6.8%, 4.1%, and 2% of cases respectively (Tables S1–S3). Whether AMPK amplification equates to increased activity remains to be determined, however AMPK phosphorylation/activation is reported to positively correlate with Gleason score and disease progression [205,206].

Interestingly, androgen-mediated activation of AMPK has been shown to increase the growth of prostate cancer cells, associated with elevated intracellular ATP levels and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1$\alpha$)-mediated mitochondrial biogenesis [206]. Thus, AR-mediated AMPK activation could potentially function to avoid energy crisis and promote tumor growth. Upstream activators of AMPK include Ca$^{2+}$/calmodulin-dependent protein kinase kinase $\beta$ (CAMKK$\beta$), liver kinase B1 (LKB1), sestrins, and potentially mitogen-activated protein kinase kinase kinase 7 (MAP3K7) [207–209]. Below we explore several potential mechanisms underpinning deregulation of the AMPK-AKT/mTOR signaling axis in prostate cancer.

2.8.1. CAMKK$\beta$ Amplification

CAMKK$\beta$ is encoded by CAMKK2 and phosphorylates AMPK in response to Ca$^{2+}$ signaling. In prostate cancer, CAMKK2 is amplified in up to 6.3% of patients (Tables S1–S3), however it is currently unknown if CAMKK2 amplification promotes AMPK activity in the clinic. In a Pten-deleted prostate cancer mouse model, Camkk2 deletion or CAMKK$\beta$ pharmacological inhibition has been shown to suppress prostate tumorigenesis and reduce de novo lipogenesis, whereas Prkab1 (AMPK-$\beta_1$) and Pten co-deletion accelerates tumor progression [210]. These findings indicate that CAMKK$\beta$ plays an oncogenic role in this setting and that CAMKK$\beta$ and AMPK-$\beta_1$ play opposing roles in Pten-deficient prostate cancer, possibly reflecting their differential regulation of lipogenesis [210]. CAMKK$\beta$ has also been shown to activate AMPK in response to androgen signaling, and AMPK can subsequently inhibit AR function to form a negative feedback loop [210]. However, the impact on the PI3K-AKT-mTOR signaling cascade remains unclear. Interestingly, a recent report has shown that CAMKK$\beta$ can directly phosphorylate AKT at residue Thr308 in ovarian cancer cells [211], indicating CAMKK$\beta$ may regulate AKT/mTOR signaling both directly and indirectly via AMPK.

2.8.2. LKB1 Loss

LKB1 (encoded by serine/threonine kinase 11, STK11) is a multifaceted enzyme that plays a tumor suppressive role by phosphorylating multiple substrates (e.g., AMPK and PTEN) to regulate crucial cellular processes including cell metabolism, polarity, differentiation, and proliferation [212,213] (Figure 1). While STK11 deletion or inactivating mutations are frequent in lung cancer (occurring in up to 50% of patients) [208], STK11 mutations are rare in prostate cancer (0.2% incidence, Tables S1–S3) and the frequency of STK11 deep deletion is also comparatively low (0–3.4% incidence, Tables S1–S3). We have previously shown that LKB1 exerts a tumor suppressive function in the prostate, as Lkb1 homozygous deletion in murine prostate epithelial cells causes prostate intra-epithelial neoplasia (PIN), associated with elevated PI3K/AKT signaling [214]. The relatively mild effects of LKB1 loss are greatly enhanced when combined with Pten heterozygosity in the mouse prostate, which causes lethal metastatic prostate cancer [215]. Interestingly, the expression of either wild-type LKB1, or a kinase-dead form of LKB1 (LKB1$^{K78I}$) is sufficient to reduce tumor burden and impair metastatic potential of DU145.
prostate cancer cells that lack LKB1, indicating LKB1 may also elicit a kinase-independent tumor suppressive function [215]. These in vivo findings indicate that deregulation of the LKB1-AMPK signaling axis is a potential mechanism whereby AKT/mTOR signaling is potentiated to facilitate prostate tumor formation and/or progression. Furthermore, a recent study has shown that LKB1 protein levels are reduced in immortalized prostate cancer cell lines relative to normal prostate epithelial cells, and siRNA-mediated STK11 knockdown correlated with elevated hedgehog signaling and increased proliferation and invasion of prostate cancer cells in vitro, however PI3K-AKT-mTOR signaling was not assessed [216].

2.8.3. Sestrin Deletion

Sestrins are a family of stress inducible antioxidant proteins comprising of SESN1, SESN2, and SESN3, which play a key role in regulating autophagy, mitophagy, metabolic homeostasis, inflammation, hypoxia and oxidative stress [217–219]. SESN1 and SESN2 are p53 target genes that are induced upon DNA damage and oxidative stress [217]. SESN1 and SESN2 can directly bind to both the TSC1:TSC2 complex and AMPK, which leads to AMPK activation/autophosphorylation in a p53-dependent manner and stimulates AMPK-mediated phosphorylation of TSC2 to negatively regulate mTORC1 signaling [217]. In addition, sestrins are reported to negatively regulate mTORC1 signaling via GATOR2/RAG, indicating that sestrins can also mediate PI3K-AKT-mTOR signaling in response to energy stress (e.g., nutrient starvation) [220,221].

Genetic alterations in the genes encoding sestrins have been linked to non-small cell lung carcinoma (NSCLC) and colorectal cancer, and recent evidence in the literature has indicated sestrins play a tumor suppressive role [221,222]. Although sestrin mutations are rare (≤0.8%), SESN1 deep deletion is a frequent event in prostate cancer occurring in 4.7–13.4% of cases (Tables S1–S3), potentially leading to increased mTORC1 signaling through alleviation of SESN1-mediated negative regulation of mTORC1. Interestingly, similarly to FOXO3, SESN1 is located within the 6q21 locus that is commonly lost in prostate cancer [160]. SESN1 is also reported to be transcriptionally repressed by AR [223], whereas p53 and FOXOs are known to mediate SESN1 transcription [156,217]. Thus, future work exploring the functional significance and predictive value of SESN1 depletion in prostate cancer could identify new therapeutic avenues or biomarkers to aid patient care.

2.8.4. MAP3K7 Deletion

MAP3K7 (also known as transforming growth factor (TGF) β-activated kinase 1, TAK1) is a serine/threonine protein kinase that mediates cell survival via NF-κB-dependent and NF-κB-independent signaling in response to TGFβ and cytokines [224]. Recent evidence in the literature has indicated that MAP3K7 may also mediate AMPK-AKT-mTOR signaling, as MAP3K7/TAK1 inactivation is associated with AMPK activation and reduced p-mTOR levels in skeletal muscle [209]. However, MAP3K7 is reported to mediate mTOR signaling independently of AMPK in hepatocellular carcinoma, possibly via p38 activation [225].

In prostate cancer, MAP3K7 is a putative tumor suppressor gene and MAP3K7 deletion has been shown to directly correlate with prostate cancer progression, lymph node metastasis, and biochemical recurrence [226,227]. MAP3K7 deep deletion is a frequent event in prostate cancer, occurring in up to 14.8% of patients (Tables S1–S3). Furthermore, loss of Map3k7 in mice has been shown to promote prostate tumorigenesis [227], suggesting MAP3K7 plays a tumor-suppressive function in the prostate. However, in an AML xenograft model MAP3K7 inhibition was found to attenuate leukemia development [228], indicating that MAP3K7 plays a dual role as a tumor suppressor and an oncogene depending on the malignancy.
3. The PI3K-AKT-mTOR Pathway Intersects with Multiple Oncogenic Signaling Cascades to Facilitate Prostate Cancer Growth

The PI3K-AKT-mTOR signaling cascade is one of the most frequently upregulated pathways in prostate cancer, which potentiates multiple downstream signaling events to mediate a plethora of cellular processes that promote tumor growth and therapeutic resistance to current treatment regimens. Targeting the PI3K-AKT-mTOR pathway using small molecules, such as pan-PI3K, PI3K-isofrom specific, AKT, mTOR and dual PI3K/mTOR inhibitors has been challenging owing to their limited efficacy and poor tolerability (reviewed in [14–17,134,229,230]). Many clinical trials involving PI3K-AKT-mTOR-directed therapies have failed owing to incomplete inhibition of the pathway, reflecting the multiple modes of pathway redundancy and numerous positive feedback loops that exist both within the PI3K-AKT-mTOR cascade and via crosstalk with other signaling pathways [15,231–236] (Figure 1). Here, we review PI3K-AKT-mTOR interactions with the RAS/MAPK, AR, and WNT signaling pathways, illustrating the need to improve our molecular understanding of the broader PI3K-AKT-mTOR signaling network. Delineating the complexity of the PI3K-AKT-mTOR pathway interactions with other signaling cascades during normal tissue homeostasis, tumorigenesis and therapeutic resistance is crucial for the discovery of new, efficacious personalized treatment approaches that overcome PI3K-AKT-mTOR inhibitor resistance.

3.1. PI3K-AKT-mTOR and RAS/MAPK Signaling Crosstalk

The RAS/MAPK cascade transduces extracellular growth signals via transmembrane receptors (e.g., RTKs and GPCRs) and a series of intracellular protein kinases to regulate gene expression in the nucleus, and to mediate a range of cellular functions including cell proliferation, migration, differentiation, senescence, and survival [25,237,238]. Growth factors bind to the extracellular surface of RTKs (e.g., epidermal growth factor receptor, EGFR, and fibroblast growth factor receptor, FGFR) leading to a conformational change that enables RTK dimerization and autophosphorylation of several tyrosine residues within the RTK cytoplasmic tail. This creates docking sites for adaptor proteins that stimulate downstream effector cascades, such as growth factor receptor-bound protein 2 (GRB2) that recruits Son of Sevenless (SOS) and the GTPase RAS to activate the MAPK cascade (RAF-MEK-ERK signaling) and drive transcription of RAS/MAPK target genes [237,238] (Figure 1).

The RAS/MAPK cascade is frequently deregulated in human cancers, including prostate cancer [238]. Activating genetic alterations (i.e., mutation/amplification) in RAS (HRAS, NRAS, or KRAS) and BRAF have been reported in primary and metastatic prostate cancer (1–8% incidence), and augmented MAPK signaling is reported to correlate with castration-resistance and metastatic progression [43,45,46,101,239]. The PI3K-AKT-mTOR and RAS/MAPK pathways are interconnected at multiple levels (Figure 1), predominantly owing to (a) shared upstream regulation mechanisms through RTKs/GPCRs and their associated adaptors, (b) the ability of respective cytosolic signaling components to interact and cross-regulate, and (c) the regulation of joint downstream targets (e.g., BAD and RPS6), reviewed in [25,240]. At the level of the receptor for example, the GRB2-SOS complex that is recruited to activated RTKs can bind to the scaffolding protein GAB1 (GRB2-associated binder-1), which interacts with RasGAP, SHP2, PI3K, and PIP3 to augment both RAS/MAPK and PI3K-AKT-mTOR signaling [25]. In addition, mTORC1 signaling can negatively regulate RTK signaling to reduce both PI3K-AKT-mTOR and RAS/MAPK activity, including mTORC1-S6K-mediated suppression of the insulin receptor substrate protein IRS1; a major IGF-1 receptor substrate and adaptor protein that can promote both PI3K and RAS activation by binding to p85 and GRB2 respectively [25,241]. S6K can also phosphorylate RICTOR to reduce mTORC2 signaling [25,242].

At the membrane, RAS-GTP can also bind to the RAS-binding domain (RBD) of p110α, p110δ, and p110γ to directly activate several Class I PI3K catalytic subunit isoforms [20,243]. Intracellular components of both cascades also interact to form multiple feedforward and feedback loops that enable PI3K-AKT-mTOR and RAS/MAPK pathway cross-regulation (Figure 1) [25,232,240]. For instance, RAS/MAPK activation has been shown to stimulate mTORC1 signaling through ERK, which can...
directly phosphorylate TSC2, RAPTOR and 90 kDa ribosomal S6 kinase (RSK) to inactivate/dissociate the TSC1:TSC2 complex and regulate the recruitment of mTORC1 substrates [244–246]. ERK-RSK signaling can also phosphorylate serum response factor (SRF), cAMP response element-binding protein (CREB) and RPS6, thus promoting cap-dependent translation independently of mTORC1-S6K signaling [247,248]. In addition, AKT is also reported to directly phosphorylate and negatively regulate RAF to suppress the MAPK cascade [249,250], and activated RAS has recently been shown to directly interact with mSIN1 to stimulate mTORC2 signaling in cancer cells (including prostate cancer cell lines) [251].

3.1.1. RAS/MAPK-PI3K-AKT-mTOR Interactions Promote Resistance to PI3K-AKT-mTOR Pathway-Directed Therapies

Clinical trials exploring the efficacy of inhibitors targeting the PI3K-AKT-mTOR pathway in prostate cancer have been extensively reviewed previously [14–17]. Despite promising results in early preclinical studies [252,253], allosteric mTORC1 inhibitors (e.g., rapamycin and rapamycin analogs/rapalogs such as Everolimus and Temsirolimus) have been ineffective in patients with prostate cancer, owing to their inability to suppress AKT activity and a number of adverse side effects [17,254]. Evidence in the literature has revealed several mechanisms of resistance, including activation of the RAS/MAPK pathway [235,255–257]. Both normal and transformed prostate epithelial cells have been shown to augment RAS/MAPK signaling in response to mTORC1 inhibition [235,255], and administration of Everolimus (RAD001) has been shown to induce MAPK signaling in a Pten-deleted mouse model of prostate cancer [235,255]. Although the mechanisms underpinning resistance to mTORC1 inhibitors are not completely understood, several signaling events that involve PI3K/AKT and RAS/MAPK crosstalk have been identified. For instance, mTORC1 inhibition is reported to promote AKT and RAS/MAPK signaling by blocking mTORC1-S6K-mediated negative regulation of IRS1 and mTORC2 signaling [258,259] (Figure 2A). Inhibition of mTORC1 has also been shown to prevent mTORC1 stabilization of growth factor receptor bound protein 10 (GRB10), an RTK adaptor protein that negatively regulates RTK signaling [260]. Resistance to AKT inhibitors (e.g., capivasertib and ipatasertib) has also been linked to elevated RAS/MAPK signaling and mTORC2 activity [14,261]. AKT inhibition can lead to the nuclear accumulation of active FOXO1, resulting in increased transcription of FOXO1-regulated genes, such as ERBB2/3 that encode human epidermal growth factor 2/3 (HER2/3) RTKs [25,237,262–264] (Figure 2B). PI3K inhibition with either pan-PI3K inhibitors (GDC0941 and XL-147) or a dual PI3K/mTOR inhibitor (BEZ235) has also been found to increase HER2/3 expression in breast cancer, resulting in increased RAS/MAPK signaling [265,266]. Furthermore, FOXO-dependent transcription is associated with p110α and PDK1 co-inhibition [145]. Additionally, the mTORC2 substrate SGK1 can replace AKT in response to PI3K/AKT inhibition, leading to the activation of shared AKT substrates that mediate oncogenic cellular processes such as cell growth, survival metabolism, and migration [145,267] (Figure 2B). In PIK3CA mutant breast cancer cells, PDK1-SGK1 signaling has been shown to sustain AKT-independent mTORC1 activation to promote resistance to the p110α-isoform-specific PI3K inhibitor BLY719, and PDK1 or SGK1 blockade can restore BLY719 sensitivity [145]. Furthermore, elevated SGK1 can predict for AKT inhibitor resistance in breast cancer cells [267]. Interestingly, Class I PI3K and AKT inhibition has also been shown to increase PI3K Class III hVsp34-SGK3 signaling in breast cancer cells, which can substitute for AKT by phosphorylating TSC2 to activate mTORC1 [148]. Whether SGK1/3 shares AKT’s ability to phosphorylate and activate RAF is currently unknown.
prostate cancer, owing to their inability to suppress AKT activity and a number of adverse side effects [17,254]. Evidence in the literature has revealed several mechanisms of resistance, including activation of the RAS/MAPK pathway [235,255–257]. Both normal and transformed prostate epithelial cells have been shown to augment RAS/MAPK signaling in response to mTORC1 inhibition [235,255], and administration of Everolimus (RAD001) has been shown to induce MAPK signaling in a Pten-deleted mouse model of prostate cancer [235,255]. Although the mechanisms underpinning resistance to mTORC1 inhibitors are not completely understood, several signaling events that involve PI3K/AKT/PI3K and RAS/MAPK crosstalk have been identified. For instance, mTORC1 inhibition is reported to promote AKT and RAS/MAPK signaling by blocking mTORC1-S6K-mediated negative regulation of IRS1 and mTORC2 signaling [258,259] (Figure 2A). Inhibition of mTORC1 has also been shown to prevent mTORC1 stabilization of growth factor receptor bound protein 10 (GRB10), an RTK adaptor protein that negatively regulates RTK signaling [260].

Figure 2. PI3K-AKT-mTOR and RAS/MAPK pathway crosstalk can contribute to mTORC1 and AKT inhibitor resistance. Model schematics illustrating reported mechanisms of therapeutic resistance to (A) mTORC1 inhibition and (B) AKT inhibition. mTORC1 and AKT blockade potentiates a series of feedback/feedforward loops between the PI3K-AKT-mTOR and RAS/MAPK signaling pathways, leading to augmented RAS/MAPK signaling and incomplete suppression of the PI3K-AKT-mTOR cascade that can promote drug-resistant tumor growth. AKTi, AKT inhibitor; mTORC1i, mTORC1 inhibitor.

3.1.2. Co-targeting RAS/MAPK and PI3K-AKT-mTOR Signaling in Prostate Cancer

Co-activation of the RAS/MAPK and PI3K-AKT-mTOR signaling pathways occurs frequently in human malignancies including prostate cancer, thus considerable research has been devoted to establishing how these two oncogenic cascades interact [101,256,257,268–270]. Nearly all metastatic prostate cancer patients are reported to show deregulation of both cascades [43]. To model this in vivo, genetically engineered mouse models of prostate cancer with prostate specific Pten homozygous deletion harboring either a KrasG12D activating mutation or oncogenic BRafV600E with NK3 Homeobox 1 (Nkx3.1) depletion, promotes rapid tumor growth and metastatic progression relative to the single mutants [101,268,269]. To our knowledge, these tumor models were the first immunocompetent transgenic mouse models of prostate adenocarcinoma to display reproducible metastatic disease. Taken together, these findings indicate that PI3K-AKT-mTOR and RAS/MAPK signaling synergize to promote prostate cancer growth and metastatic progression, and given the frequency of co-activation of these cascades in the clinic, this provides a clear justification for exploring the combination of PI3K-AKT-mTOR and RAS/MAPK pathway inhibitors in patients with advanced prostate cancer. This notion is further supported by the fact that MEK inhibition is associated with elevated PI3K-AKT-mTOR signaling in mammalian cancer cells, including prostate cancer cells [271,272]. Preclinical studies have also shown that co-inhibition of MEK and mTORC1 can significantly reduce tumor burden relative to monotherapy in a mouse model of prostate cancer driven by simultaneous heterozygous deletion of
**Nkx3.1 and Pten** [256], and can inhibit cell growth and increase cytotoxicity in the castration-resistant CWR22Rv1 human prostate cancer cell line [272]. However, MEK inhibition alone is reported to be sufficient to suppress the metastatic spread of Pten-deleted and KRas activated stem/progenitor murine prostate cancer cells orthotopically transplanted in vivo, similarly to combined mTORC1 and MEK inhibition [101]. This highlights the need to improve our molecular understanding of how these cascades interact during disease progression and in the presence of different genetic drivers to aid the stratification of patients that will benefit from (a) PI3K-AKT-mTOR inhibition, (b) MEK inhibition or (c) combined PI3K-AKT-mTOR and RAS/MAPK blockade.

Several prostate cancer clinical trials have been designed to investigate the therapeutic efficacy of targeting MEK (e.g., MEK1/2 inhibitor trametinib, ClinicalTrials.gov identifiers: NCT02881242 and NCT01990196) or the PI3K-AKT-mTOR cascade (e.g., pan-AKT inhibitors including ipatasertib and capivasertib, ClinicalTrials.gov identifiers: NCT01485861/NCT03673787 and NCT02525068/NCT02121639 respectively) [134,273]. Metformin (an oral type 2 anti-diabetic drug) is also currently being investigated in prostate cancer within the STAMPEDE trial [274]. Metformin targets the mitochondrial respiratory chain complex I, leading to reduced mitochondrial ATP production that causes cellular energy crisis with subsequent AMPK activation and mTORC1 inhibition [275]. Metformin has also been shown to inhibit MEK/ERK in response to growth factors, contrasting mTORC1 inhibitor treatment with rapamycin that increases MAPK signaling [276].

Although not currently specific to patients with prostate cancer, clinical trials exploring co-inhibition of the PI3K-AKT-mTOR and MAPK cascades to treat various advanced solid cancers have also been developed (e.g., ClinicalTrials.gov identifiers: NCT01390818, NCT01347866, and NCT02583542), although response rates appear to be low and are linked to RAS and RAF mutations [277]. For example, a recent Phase Ib study of combination therapy with the MEK1/2 inhibitor binimetinib (Mektovi) and the pan-PI3K inhibitor Buparlisib (BKM120) in advanced solid tumors reported promising efficacy in patients with advanced ovarian cancer with RAS/RAF genetic alterations, however continuous dosing resulted in intolerable toxicities and an intermittent schedule is suggested for future trials [278]. Additionally, the MATCH screening trial (targeted therapy directed by genetic testing in treating patients with advanced refractory solid tumors, lymphomas, or multiple myeloma, ClinicalTrials.gov identifier: NCT02465060) will investigate the efficacy of MEK and PI3K inhibitors as monotherapies in patients with progressive disease that carries a genetic alteration in either the RAS/MAPK or the PI3K-AKT-mTOR pathways respectively.

### 3.2. PI3K-AKT-mTOR and AR Signaling Crosstalk

AR signaling regulates cell growth, differentiation, migration and survival, and plays a critical role as a transcriptional regulator during prostate development, normal prostate tissue homeostasis, and prostate cancer [279–281]. AR is a steroid nuclear receptor that transmits androgen signals such as testosterone (T), or its more potent metabolite dihydrotestosterone (DHT), to regulate gene expression and coordinate cellular responses. T is derived from cholesterol through a cascade of biochemical reactions involving four enzymes: cytochrome P450 side-chain cleavage enzyme (P450scc), cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1), 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) [282]. The conversion of cholesterol to pregnenolone is catalyzed by P450scc, and its subsequent conversion to progesterone is catalyzed by 3β-HSD. Pregnenolone and progesterone can be converted by CYP17A1 to 17-OH-pregnenolone and 17-OH-progesterone and subsequently to dehydroepiandrosterone (DHEA) and androstenedione (AD or A4). DHEA and AD may then be converted to androstenediol and T by 17β-HSD [282]. T synthesis and secretion predominantly occurs in the Leydig cells of the testes, and is stimulated by pituitary-derived luteinizing hormone (LH), which is secreted in response to hypothalamus-derived LHRH, (also known as gonadotrophin-releasing hormone, GnRH) [281,283]. In the prostate, 5-alpha-reductase converts T to DHT [281,283]. In addition, androgens can also be produced by
the adrenal glands and in some instances by prostate tumor cells [284], which may contribute to prostate cancer growth post-orchiectomy [285].

In the absence of androgens, AR forms a cytoplasmic complex with chaperones (e.g., HSP90 and HSP70). Androgen binding displaces the chaperones and triggers a conformational change in AR, which enables AR homodimerization and nuclear translocation (Figure 1) [279,281,286]. Nuclear AR homodimers regulate the transcription of androgen-regulated genes (e.g., SLC43A1, FKBP5, CAMKK2, NKX3.1 and KLK3) by directly binding to an androgen responsive element (ARE) in the promotor/enhancer region of target genes [279,286]. However, growth factors (e.g., EGF and IGF-1), cytokines (e.g., IL6) and intracellular signaling kinases (e.g., AKT and SRC) can also independently stimulate AR dependent transcriptional activity when androgen levels are low, which can facilitate therapeutic resistance to androgen/AR blockade [12,281,287]. In addition to regulating gene transcription, AR can also mediate a number of intracellular signaling pathways through direct protein–protein interactions within the cytoplasm (known as non-genomic AR signaling) [12,288].

Aberrant AR signaling is a common feature of prostate cancer [289], with up to 56% of primary cases and 100% of metastatic cases reported to carry genetic alterations within key AR pathway components [43]. While the majority of men with prostate cancer initially respond to androgen/AR-directed therapy, they inevitably develop castration-resistant prostate cancer (CRPC), as malignant cells develop therapeutic resistance [5,290]. Several inherent and acquired resistance mechanisms have been identified, including AR genetic alterations (e.g., activating mutations, gene amplification, androgen-independent constitutively active splice variants, AR loss), augmented androgen biosynthesis, adrenal androgens, AR-bypass signaling (e.g., glucocorticoid receptor (GR) regulation of shared AR target genes), trans-differentiation to neuroendocrine prostate cancer and ligand-independent activation via crosstalk with another signaling cascade, such as the PI3K-AKT-mTOR pathway [12,283].

The PI3K/AKT/mTOR and AR pathways have been shown to cross-regulate through several reciprocal inhibitory loops [11,12,24] (Figure 3). Consequently, the PI3K-AKT-mTOR pathway can be inadvertently activated in response to androgen/AR-directed therapies, and vice versa PI3K-AKT-mTOR pathway inhibition can augment AR signaling, leading to therapeutic resistance. Human patient samples (both primary tumor and bone metastases), human prostate cancer cell lines and transgenic mouse models of prostate cancer have consistently demonstrated that AKT-mTOR signaling is increased in response to androgen/AR-directed blockade [11,13,24,291–293]. Mechanistically, it is reported that inhibiting AR signaling reduces expression of the AR target gene FK506-binding protein-5 (FKBP5), which leads to PHLPP destabilization and reduced PHLPP-mediated dephosphorylation of AKT at Ser473 to promote AKT signaling [11,24] (Figure 3A). Thus, compensatory activation of the PI3K-AKT-mTOR pathway in response to androgen/AR pathway inhibition can facilitate CRPC growth.

Conversely, PI3K-AKT-mTOR pathway inhibition is associated with augmented AR signaling that can contribute to drug resistance and promote prostate cancer progression [11,293–295]. Carver and colleagues showed that PI3K/mTOR inhibition activates AR signaling in human xenograft and transgenic mouse models of prostate cancer, and that co-treatment with the PI3K/mTOR inhibitor BEZ235 and the antiandrogen MDV3100 (enzalutamide) significantly reduced tumor burden relative to monotherapy [11]. In corroboration, resistance to the AKT inhibitor capivasertib (AZD5363) in LNCaP prostate cancer xenografts is also associated with elevated AR signaling, and combining AZD5363 treatment with the antiandrogen bicalutamide prolonged disease stabilization [295]. Furthermore, mTOR and EGFR co-inhibition with everolimus and gefitinib has shown limited sensitivity in patients owing to enhanced AR activity and PSA levels [293], providing further rationale for combining AR and PI3K-AKT-mTOR blockade to treat prostate cancer.
Despite the antagonistic crosstalk between AR and AKT (Figure 3), AR signaling can boost mTORC1 activation through an AR-dependent increase in amino acid transport during tumorigenesis [304]. AR mediates expression of L-type amino acid transporters (e.g., LAT3 encoded by SLC43A1) to maintain sufficient levels of leucine needed for mTORC1 signaling and cell growth (Figures 1 and 3) [304]. Moreover, LAT1 and LAT3 transport inhibition is sufficient to decrease cell growth and mTORC1 signaling in prostate cancer cells in vitro [304]. Recent in vitro data have also revealed that mTOR can directly interact with AR in the nucleus of prostate cancer cells to promote metabolic rewiring, and high levels of nuclear mTOR correlate with poor prognosis in patients with prostate cancer [293]. Additionally, AKT has been shown to directly bind and phosphorylate AR when T levels are low, although the functional significance of this event remains to be determined [16,305,306].

The reciprocal feedback loop between AR and PI3K-AKT-mTOR signaling may also be perturbed by Speckle-type BTB/POZ protein (SPOP) loss of function mutations that lead to the stabilization of the SPOP substrate SRC3 (e.g., p.F133V), which consequentially increases PI3K activity [307]. SPOP is an adaptor protein of the Cullin 3 family E3 ligases that can target SRC3 for ubiquitination and proteasomal degradation.

Several distinct molecular mechanisms have been identified that underpin AR reactivation upon AKT inhibition. Notably, AKT inhibition can prevent AKT-mediated nuclear exclusion of FOXOs, which can lead to augmented transcription of FOXO-target genes such as RTKs (e.g., ERBB2/3 encoding HER2/3) (Figure 3B) [11,262,296]. HER2/3 activity has been shown to promote AR signaling by protecting AR from ubiquitination and proteasomal degradation, and by enhancing AR binding to ARE target sequences and stimulating AR transcriptional activity [297–299] (Figure 3B). Nonetheless, the role of FOXO-dependent signaling in PI3K-AKT-mTOR and AR pathway crosstalk is complex. Although FOXO transcription factors upregulate the expression of RTKs [262] causing a subsequent increase in AR signaling [298], the ectopic expression of FOXO1 conversely dampens AR activity, which is further exacerbated when FOXO1 is co-transfected with the AR coregulator HDAC3 [300].

PTEN loss has also been shown to downregulate AR signaling via the upregulation of several factors that inhibit AR signaling through histone modification mechanisms such as early growth response 1 (EGR1), transcription factor AP-1 (c-JUN), and the catalytic subunit of polycomb repressive complex 2 enhance of zeste homolog 2 (EZH2) (Figure 1) [24]. PTEN protein-phosphatase activity has...
also been shown to protect the tumor suppressor NK3 homeobox 1 (NKX3.1) from degradation, which can derail the AR transcriptional network [301]. Of note, NKX3.1 and AR can cross-regulate [302], and enforced NKX3.1 expression can suppress Pten-deleted prostate tumorigenesis in transgenic mice [303].

Despite the antagonistic crosstalk between AR and AKT (Figure 3), AR signaling can boost mTORC1 activation through an AR-dependent increase in amino acid transport during tumorigenesis [304]. AR mediates expression of L-type amino acid transporters (e.g., LAT3 encoded by SLC43A1) to maintain sufficient levels of leucine needed for mTORC1 signaling and cell growth (Figures 1 and 3) [304]. Moreover, LAT1 and LAT3 transport inhibition is sufficient to decrease cell growth and mTORC1 signaling in prostate cancer cells in vitro [304]. Recent in vitro data have also revealed that mTOR can directly interact with AR in the nucleus of prostate cancer cells to promote metabolic rewiring, and high levels of nuclear mTOR correlate with poor prognosis in patients with prostate cancer [293]. Additionally, AKT has been shown to directly bind and phosphorylate AR when T levels are low, although the functional significance of this event remains to be determined [16,305,306].

The reciprocal feedback loop between AR and PI3K-AKT-mTOR signaling may also be perturbed by Speckle-type BTB/POZ protein (SPOP) loss of function mutations that lead to the stabilization of the SPOP substrate SRC3 (e.g., p.F133V), which consequentially increases PI3K activity [307]. SPOP is an adaptor protein of the Cullin 3 family E3 ligases that can target SRC3 for ubiquitin-mediated degradation and a known tumor suppressor [12,308–310]. In prostate cancer, SPOP is frequently mutated (9–11% incidence) [45,46]. Remarkably, SPOP mutation can also stabilize AR and potentiate AR signaling whilst the PI3K-AKT-mTOR signaling pathway is activated, allowing coordinated and cooperative signaling that drives tumorigenic growth [307]. Conversely, wildtype SPOP can trigger E3 ligase mediated degradation of AR via hinge domain binding when androgens levels are low [311]. Furthermore, AR has been shown to positively regulate the PI3K-AKT-mTOR pathway via a direct interaction with the SH2 domain of the Class IA PI3K regulatory subunit p85α, which has been shown to activate the PI3K-AKT-mTOR cascade [312], further highlighting the complexity of the interactions between these two cascades.

Taken together, these findings support the rationale for combining pharmacological inhibition of the AR and PI3K-AKT-mTOR cascades to treat prostate cancer in the clinic, and highlight the need for further work to delineate the molecular mechanisms underpinning crosstalk between these two oncogenic cascades. Importantly, clinical trials exploring co-targeting AR and PI3K-AKT-mTOR signaling are beginning to show promise. A randomized Phase Ia/II study combining the pan-AKT inhibitor ipatasertib with abiraterone in mCRPC patients has reported ipatasertib + abiraterone prolongs radiographic progression-free survival (rpFS), improves overall survival and extends time to PSA progression compared to abiraterone alone, particularly in patients with PTEN loss (ClinicalTrials.gov identifier: NCT01485861) [134]. This study also reports that the adverse effects common to PI3K-AKT-mTOR blockade (e.g., hyperglycemia) were generally clinically manageable [134]. A Phase I dose escalation study combining enzalutamide and capivasertib to treat mCRPC has also recently reported 3/16 patients responded (ClinicalTrials.gov identifier: NCT02525068) [313]. In this study, patients who met the response criteria had PTEN loss or AKT activating mutations, low/absent AR-V7 protein levels and elevated p-ERK [313]. Nevertheless, several additional clinical trials investigating the combination of AR and PI3K-AKT-mTOR blockade in men with mCRPC did not demonstrate a therapeutic benefit and were associated with poor tolerability (ClinicalTrials.gov identifiers: NCT01385293, NCT01634061 and NCT01717898) [314–316]. Interestingly, D’Abronzo and colleagues also recently showed that elF4E phosphorylation at residue Ser209 in human CRPC cell lines pre-treated with the antiandrogen bicalutamide underpins resistance to subsequent combination therapy with bicalutamide + rapamycin treatment. Remarkably, suppression of elF4E phosphorylation by MNK1/2 (MAP kinase interacting serine/threonine kinase1/2) or ERK1/2 inhibition was shown to sensitize bicalutamide pre-treated CRPC cells to combined anti-androgen and mTORC1 blockade [317], presenting a novel avenue for overcoming therapeutic resistance. Thus, despite some promising results, it is evident that further investigation into the molecular mechanisms underpinning AR and
PI3K-AKT-mTOR pathway crosstalk in prostate cancer is required to improve patient stratification and to discover new therapeutic approaches and predictive biomarkers that can inform future clinical trial design.

3.3. PI3K-AKT-mTOR and WNT Signaling Interactions

The WNT family is an evolutionarily conserved group of proteins essential for growth control, organ development, tissue homeostasis and stem cell renewal in multiple organs, and is crucial for normal prostate development [318,319]. WNT signaling is potentiated by secreted WNT ligands (a family of 19 lipoglycoproteins) that bind extracellularly to transmembrane frizzled receptors (FZD1-10) and their co-receptors, such as low-density lipoprotein receptors (e.g., LRP5 and LRP6), tyrosine protein-kinases (e.g., receptor tyrosine kinase–like orphan receptor-1 and -2, ROR1, AR) an attractive therapeutic target for advanced prostate cancer. In addition, localized and advanced prostate cancer, and oncogenic deregulation of core WNT pathway and resistance to anti-androgens and PI3K-AKT-mTOR pathway has also been shown to mediate β-catenin localization [335], and several

PP2A activity [335]. PP2A is known to negatively regulate AKT, however it is currently speculated that this phosphatase may also directly dephosphorylate and activate β-catenin [335]. Additionally, the PI3K-AKT-mTOR pathway has also been shown to mediate β-catenin localization [335], and several
transcription factors that directly interact with β-catenin are co-regulated by the PI3K-AKT-mTOR pathway, such as FOXO3α [336] and SOX4 [337]. In prostate cancer cells, FOXO3α has been shown to suppress β-catenin transcriptional activity and can be inhibited by AKT [336], whereas SOX4 is a positive regulator of canonical WNT and is stimulated by AKT [338] (Figure 4).

**Figure 4.** PI3K-AKT-mTOR and WNT signaling crosstalk. Upon ligand binding (WNT ON), the destruction complex is recruited to the plasma membrane leading to β-catenin accumulation in both the cytoplasm and nucleus, where it activates gene expression through TCF binding. Insert illustrates WNT signaling in the absence of WNT ligand (WNT OFF). The interplay between PI3K-AKT-mTOR and WNT may occur through shared pathway components (e.g., GSK3β, PTEN, PP2A) and/or the joint regulation of transcription factors such as MYC, FOXO3α, SOX4 or YAP/TAZ. CDK4, cyclin-dependent kinase 4; LATS1/2, 1-type amino acid transporter 1/2; LDHA, 1-lactate dehydrogenase A chain; SLC2A3, solute carrier family 2, facilitated glucose transporter member 3 (encoding GLUT3, glucose transporter 3); TAZ, transcriptional co-activator with PDZ-binding motif; TEAD, transcriptional enhanced associate domain transcription factor; YAP, Yes-associated protein.

In addition to transmitting canonical WNT signals, β-catenin also form adherens junctions with α-catenin and E-cadherin at cell–cell junctions to maintain tissue architecture and facilitate cell–cell signaling (Figure 4). PTEN has also been shown to modulate β-catenin nuclear localization and transcriptional activity through caveolin-1 (CAV1)-dependent dissociation of β-catenin from E-cadherin at the membrane independently of PI3K-AKT-GSK3β signaling, leading to increased tumor formation and metastatic progression in melanoma [339].

Crosstalk between the PI3K-AKT-mTOR and WNT/β-catenin signaling pathways is also mediated via GSK3β and the TSC1:TSC2 complex [167] (Figure 4). GSK3β play a critical role in both cascades, serving as a core member of the β-catenin destruction complex that helps to maintain low level of cytosolic/nuclear β-catenin in the absence of WNT signal [340], and as a direct substrate of AKT [167]. AKT inactivates GSK3β by phosphorylating residue Ser9 [167]. GSK3β can also phosphorylate and activate TSC2 resulting in inhibition of mTOR activity [167], and can restrict cellular growth by suppressing glucose uptake via TSC2 and mTOR [341]. Active WNT signaling inhibits GSK3β, abrogates the suppression of mTOR and stimulates phosphorylation of S6K, S6, and eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) [167]. Interestingly, in the absence of TSC1 or TSC2, S6K has also been shown to inactivate GSK3β by directly phosphorylating residue Ser9 and
active GSK3β has also been shown to phosphorylate/activate S6K, adding further complexity to GSK3β signaling between the WNT and PI3K-AKT-mTOR cascades [342]. However, previous work has also indicated that GSK3β does not mediate crosstalk between the PI3K-AKT-mTOR and WNT/β-catenin pathways [343,344], raising the possibility that GSK3β function is context/tissue dependent. Of note, WNT ligands can also activate mTOR through MYC-dependent suppression of TSC2 [345].

PI3K-AKT-mTOR and WNT signaling may also interact through Hippo signaling. Hippo signaling is tightly intertwined with cell size regulation and nutrient sensing through LKB1-AMPK, TSC1:TSC2 and mTOR [346,347], and the Hippo pathway signaling proteins yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are integral parts of both canonical and non-canonical WNT signaling [348,349]. YAP and TAZ are members of the β-catenin destruction complex, and in the presence of WNT signals, they dissociate from the complex and translocate to the nucleus to activate downstream targets [348] (Figure 4). AMPK activation has also been shown to negatively regulate YAP/TAZ activity [347].

Non-canonical WNT signaling has also been shown to activate the PI3K-AKT-mTOR pathway. For example, WNT/FZD7-dependent dissociation of Gβγ from Gai enhances PI3K-AKT signaling and increases tumor cell invasive potential [350]. ROR1 can also activate PI3K-AKT signaling in response to trans-phosphorylation by tyrosine kinases, such as MET and SRC [351]. In addition, WNT receptor Frizzled2 (FZD2) can drive epithelial-to-mesenchymal transition (EMT) and cell migration through activation of Fyn [352], and activated Fyn kinase activity has been shown to suppress the AMPK-LKB1 signaling axis by blocking LKB1 redistribution into the cytoplasm [353].

Interestingly, the PI3K-AKT-mTOR, WNT, MAPK and AR signaling cascades all converge to regulate the transcription factor MYC, which is frequently amplified in prostate cancer/mCRPC [44,45,354]. While MYC is a WNT/β-catenin target gene [355], PI3K-AKT-mTOR signaling can mediate MYC mRNA stability, translation and protein stability [356–360]. AR signaling has also been shown to stimulate MYC in AR-driven prostate cancer, while in normal prostate tissue AR silences MYC to maintain normal homeostasis [361,362]. However, MYC is also reported to antagonize AR transcriptional activity in prostate cancer [363]. MYC upregulation is frequently observed in prostate cancer, and although targeting MYC remains a clinical challenge, preclinical studies have emphasized the potential efficacy of MYC blockade for patients with late-stage prostate cancer [364].

WNT inhibitors are beginning to enter clinical trials, including small-molecule inhibitors to the enzyme porcupine that block WNT ligand secretion, such as WNT974 (LGK974) [320,322]. Preliminary data from a WNT974 phase 1 clinical trial (NCT01351103) for a small range of human malignancies (excluding prostate cancer) report a manageable safety profile and suppression of canonical WNT/β-catenin target gene AXIN2 [320], and recent preclinical studies have indicated that WNT974 treatment is efficacious against prostate cancer [331,365]. β-catenin has also been reported to facilitate resistance to PI3K and AKT inhibition in colon cancer [334]. Thus, further work exploring the therapeutic benefit of targeting the WNT pathway in prostate cancer is warranted.

4. Conclusions

In summary, the PI3K-AKT-mTOR cascade is frequently activated in prostate cancer, and genomic profiling has revealed that oncogenic genetic alterations occur within a diverse array of PI3K-AKT-mTOR pathway components. Significant research efforts have been devoted to delineating the mode of action of several of these aberrations (e.g., PTEN deletion and PIK3CA activating mutation), however our molecular understanding of how these events differentially mediate cell signaling programs is limited, and several genetic alterations remain to be studied functionally. Future work to gain novel insight into the functional consequence of these genetic alterations in prostate cancer is necessary to (a) identify passenger vs. driver alterations, (b) establish the ability of individual aberrations to synergize with additional oncogenic events, and (c) discover their mode of action during tumor growth, metastasis and therapeutic resistance. In conjunction with genomic and transcriptomic data, establishing the frequency and impact of post-transcriptional modifications and epigenetic
events within core PI3K-AKT-mTOR pathway components during prostate tumorigenesis and disease progression/recurrence is also crucial, as these components are regulated at multiple levels and genomic/transcriptomic data do not consistently equate with protein activity.

Targeting the PI3K-AKT-mTOR pathway in prostate cancer remains a key clinical challenge. Therapeutic resistance emerges owing to various feedback/feedforward loops and redundancy mechanisms that prevent complete suppression of the pathway and cause compensatory augmentation of interacting signaling pathways, thus rationalizing the exploration of combination therapies. Encouragingly, clinical trials are beginning to report therapeutic efficacy when combining PI3K-AKT-mTOR and androgen/AR-directed therapies, particularly in patients with mCRPC that display PTEN loss. However, the mechanism of resistance to PI3K-AKT-mTOR pathway-targeted therapies is likely to vary dramatically between patients and within individual tumors owing to several factors. These include the activity status of the pathway components, the extent of intratumoral heterogeneity, the mode and concentration of upstream stimuli, the genetic alterations present and the composition of the tumor microenvironment. Furthermore, our ability to successfully translate preclinical findings to the clinic is currently hampered by the limited number of prostate cancer preclinical models available, which do not fully cover the broad range of prostate cancer subtypes or disease heterogeneity seen in the clinic. Accordingly, to discover new therapeutic approaches that increase patient response rates and overall survival, further delineation of the complex signaling network that exists within the PI3K-AKT-mTOR pathway and the interacting MAPK, AR, and WNT pathways is needed, together with the development of a wider range of preclinical models that better recapitulate the clinic and a deeper understanding of the molecular biology underpinning prostate cancer disease subtypes and tissue heterogeneity.

Supplementary Materials: Supplementary Materials can be found at http://www.mdpi.com/1422-0067/21/12/4507/s1.

Author Contributions: Conceptualization, B.Y.S. and H.B.P.; writing—original draft preparation, B.Y.S., M.S.D. and H.B.P.; writing—review and editing, B.Y.S., M.S.D., M.J.S. and H.B.P.; project administration, H.B.P.; funding acquisition, M.J.S. and H.B.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Prostate Cancer Research Centre, a charitable incorporated organization, with registered charity number 1156027 (project grant awarded to B.Y.S. and M.J.S.). M.S.D. is supported by a Knowledge Economy Skills Scholarship 2 (KESS2) Ph.D award, in partnership with Tenovus Cancer Care. H.B.P. is supported by a Cancer Research UK career development fellowship (#A27894).

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

Abbreviations

3β-HSD 3β hydroxysteroid dehydrogenase
4E-BP1 Eukaryotic translation initiation factor 4E binding protein 1
ADT Androgen deprivation therapy
AD Androstenedione
AGC cAMP-dependent, cGMP-dependent and protein kinase C
AKTi AKT inhibitor
AMP Adenosine monophosphate
AMPK 5′ AMP-activated protein kinase
APC Adenomatous polyposis coli
AR Androgen receptor
ARE Androgen responsive element
ARF1 Adenosine ribosylation factor 1
ATG14 Autophagy related 14 homolog
ATP Adenosine triphosphate
AXIN Axis inhibitor protein
BAD Bcl-2-associated death promoter
| Term          | Description                                                                 |
|--------------|-----------------------------------------------------------------------------|
| BMK-1        | Big mitogen-activated protein kinase-1                                       |
| CaMKII       | Calmodulin-dependent kinase 2                                               |
| CAMKKβ       | Ca(2+)/calmodulin-dependent protein kinase kinase β                         |
| CAV1         | Caveolin-1                                                                  |
| CDK4         | Cyclin-dependent kinase 4                                                   |
| c-JUN        | Transcription factor AP-1                                                  |
| CK1          | Casein kinase 1                                                             |
| CAN          | Copy number alteration                                                      |
| CREB         | cAMP response element-binding protein                                       |
| CRPC         | Castrate resistant prostate cancer                                          |
| CYP17A1      | Cytochrome P450 17A1                                                        |
| DEPTOR       | Dishevelled, EGL-10 and pleckstrin (DEP) domain-containing mTOR-interacting protein |
| DFCI         | Dana-Farber Cancer Institute                                                |
| DHEA         | Dehydroepiandrosterone                                                      |
| DHTDVL       | DihydrotestosteroneDisheveled                                               |
|{EIF4E}       | Eukaryotic translation initiation factor 4E                                 |
| EGF          | Epidermal growth factor                                                     |
| EGFR         | Epidermal growth factor receptor                                             |
| EGR1         | Early growth response 1                                                     |
| EMT          | Epithelial-to-mesenchymal transition                                        |
| ERG1         | ETS-related Gene 1                                                          |
| ERK1         | Mitogen-activated protein kinase 3                                          |
| ERK2         | Mitogen-activated protein kinase 1                                          |
| EZH2         | Enhancer of zeste homolog 2                                                 |
| FKBPs        | FK506 binding protein 5                                                     |
| FOXO         | Forkhead box protein O                                                      |
| FGFR         | Fibroblast growth factor receptor                                            |
| FZD          | Frizzled family receptor                                                    |
| GAB1         | GRB2-associated binder-1                                                    |
| GDP          | Guanosine diphosphate                                                       |
| GLUT3        | Glucose transporter 3                                                       |
| GnRH         | Gonadotrophin-releasing hormone                                              |
| GPCR         | G-protein coupled receptor                                                  |
| GR           | Glucocorticoid receptor                                                     |
| GRB2         | Growth factor receptor-bound protein 2                                      |
| GRB10        | Growth factor binding protein 10                                             |
| GSK3β        | Glycogen synthase kinase 3 beta                                             |
| GTP          | Guanosine triphosphate                                                      |
| HDAC3        | Histone deacetylase 3                                                      |
| HER2/3       | Human epidermal growth factor receptor 2/3                                  |
| HSD3B/17B3   | Hydroxysteroid dehydrogenase 3B/17B3                                        |
| HSP70/90     | Heat shock protein 70/90                                                    |
| IGF          | Insulin growth factor                                                       |
| IGFR         | Insulin growth factor 1                                                     |
| IHC          | Immunohistochemistry                                                        |
| IL6          | Interleukin 6                                                               |
| INPP4B       | Inositol polyphosphate 4-phosphatase type II                               |
| INPP5D       | Inositol polyphosphate-5-phosphatase D                                     |
| INPP5J       | Inositol polyphosphate-5-phosphatase J                                     |
| INPPL1       | Inositol polyphosphate phosphatase like 1                                   |
| IRS          | Insulin receptor substrate                                                  |
| IRS1         | Insulin receptor substrate protein 1                                        |
| KLK3         | Kallikrein related peptidase 3                                              |
| LAT1/2/3     | L-type amino acid transporter 1/2/3                                         |
LDHA  L-lactate dehydrogenase A chain  
LEF  Lymphoid enhancer binding factor  
LH  Luteinizing hormone  
LHRH  Luteinizing hormone-releasing hormone  
LKB1  Liver kinase B1  
LRP5/6  Low-density lipoprotein receptor-related proteins 5 and 6  
MAPK  Mitogen-activated protein kinase  
MAP3K7  Mitogen-activated protein kinase kinase kinase 7  
mCRPC  Metastatic castrate resistant prostate cancer  
MDM2  Mouse double minute 2 homolog  
MEK  Mitogen-activated protein kinase kinase  
MSKCC  Memorial Sloan Kettering Cancer Centre  
mLST8  MTOR associated protein LST8 homolog  
MMTV-PyMT  Mouse mammary tumor virus-polyoma middle tumor-antigen  
MNK1  MAP kinase interacting serine/threonine kinase 1  
MNK2  MAP kinase interacting serine/threonine kinase 2  
mSin1  Mitogen-activated protein kinase associated protein 1 (MAPKAP1)  
mTOR  Mammalian target of rapamycin  
mTORC1  Mammalian target of rapamycin complex 1  
mTORC1i  mTORC1 inhibitor  
mTORC2  Mammalian target of rapamycin complex 2  
MuSK  Muscle specific kinase  
NF-κB  Nuclear factor kappa light chain enhancer of activated B cells  
NKX3.1  NK3 Homeobox 1  
NSCLC  Non-small-cell lung carcinoma  
P  Phosphorylation event  
PDK1  Phosphoinositide-dependent kinase 1  
PGC-1α  Peroxisome proliferator-activated receptor gamma coactivator 1-alpha  
PHLPP  PH domain leucine-rich repeat protein phosphatase  
PHLPP1  PH domain and leucine rich repeat protein phosphatase 1  
PHLPP2  PH domain and leucine rich repeat protein phosphatase 2  
P  Phosphatidylinositol  
P3K  Phosphoinositide 3-kinase  
P1(3,4,5)P2  Phosphatidylinositol 3,4,5-trisphosphate  
P1(3,4)P2  Phosphatidylinositol 3,4-bisphosphate  
PIN  Prostate intra-epithelial neoplasia  
PIP2  Phosphatidylinositol 4,5-bisphosphate  
PIP3  Phosphatidylinositol 3,4,5-trisphosphate  
PPIP  Proline-rich inositol polyphosphate 5-phosphatase  
PKB  Protein kinase B, AKT  
PKC  Protein kinase  
PKCα  Protein kinase C alpha  
PLC  Phospholipase C  
PP2A  Protein phosphatase 2A  
PPP2CA  Protein phosphatase 2 catalytic subunit Alpha  
PRAS40  Proline-rich AKT substrate of 40 kDa  
PROTOR1  Protein observed with Rictor-1  
PROTOR2  Protein observed with Rictor-2  
PSA  Prostate specific antigen  
PTEN  Phosphatase and tensin homologue deleted on chromosome 10  
PTK7  Protein tyrosine kinase 7  
RAF  Rapidly accelerated fibrosarcoma  
RAG  Recombination activating genes  
RAPTOR  Regulatory-associated protein of mTOR
| Acronym | Description |
|---------|-------------|
| RBD     | Ras-binding domain |
| RHEB    | Ras homolog enriched in brain |
| RICTOR  | Rapamycin-insensitive companion of mTOR |
| ROR1/2  | Receptor tyrosine kinase–like orphan receptor-1 and -2 |
| RPS6    | Ribosomal protein S6 |
| rPFS    | Radiographic progression-free survival |
| RSK     | 90 kDa Ribosomal S6 kinase |
| RTK     | Tyrosine kinase receptor |
| RYK     | Receptor-like tyrosine kinase |
| S6K     | Ribosomal protein S6 kinase/p70 ribosomal S6 kinase |
| SESN1   | Sestrin 1 |
| SGK1    | Serum and glucocorticoid regulated kinase 1 |
| SGK2    | Serum and glucocorticoid regulated kinase 2 |
| SGK3    | Serum and glucocorticoid regulated kinase 3 |
| SH2     | Src homology 2 |
| SHIP1   | SH2 domain-containing inositol 5'-phosphatase 1 |
| SHIP2   | SH2 domain-containing inositol 5'-Phosphatase 2 |
| SLC2A3  | Solute carrier family 2, facilitated glucose transporter member 3 |
| SLC43A1 | Solute carrier family 43 member 1 |
| SOS     | Son of Sevenless |
| SPOP    | Speckle type BTB/POZ protein |
| SRC-3   | Steroid receptor co-activator 3 |
| SRF     | Serum response factor |
| SU2C-PCF IDT | Stand Up To Cancer & Prostate Cancer Foundation International Dream Team |
| T       | Testosterone |
| TAK1    | TGFβ-activated kinase 1 |
| TAZ     | Transcriptional coactivator with PDZ binding motif |
| TBC1D7  | TBC1 Domain Family Member 7 |
| TCF     | T cell Factor |
| TCGA    | The Cancer Genome Atlas |
| TEAD    | Transcriptional enhanced associate domain |
| TEL2    | Telomere length regulation protein |
| TGF     | Transforming growth factor |
| TMPRSS2-ERG | Transmembrane protease, serine 2: ETS Transcription Factor fusion |
| TRAMP   | Transgenic adenocarcinoma mouse prostate |
| TSC1    | Tuberous Sclerosis complex 1 |
| TSC2    | Tuberous Sclerosis complex 2 |
| TTI1    | TEO2 interacting protein 1 |
| Ub      | Ubiquitination event |
| ULK1    | Unc-51 Like Autophagy Activating Kinase 1 |
| UVRAG   | UV radiation resistance-associated gene; v-ATPase, Vacuolar (H+-)-ATPase |
| VPS15   | Vacuolar protein sorting 15 |
| V-ATPase | Vacuolar H+-ATPase |
| WNT     | WNT ligand |
| YAP     | Yes-associated protein |

**References**

1. Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, N.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **2014**, *136*, E359–E386. [CrossRef]
2. Jemal, A.; Fedewa, S.A.; Ma, J.; Siegel, R.; Lin, C.C.; Brawley, O.; Ward, E.M. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. *JAMA* **2015**, *314*, 2054–2061. [CrossRef]
3. Steele, C.B.; Li, J.; Huang, B.; Weir, H.K. Prostate cancer survival in the United States by race and stage (2001–2009): Findings from the CONCORD-2 study. Cancer 2017, 123, 5160–5177. [CrossRef] [PubMed]

4. Miller, K.D.; Siegel, R.L.; Lin, C.C.; Mariotto, A.B.; Kramer, J.L.; Rowland, J.H.; Stein, K.D.; Alteri, R.; Jemal, A. Cancer treatment and survivorship statistics, 2016. CA Cancer J. Clin. 2016, 66, 271–289. [CrossRef] [PubMed]

5. 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. 2018, 22, 24–38. [CrossRef] [PubMed]

6. Culig, Z. Molecular Mechanisms of Enzalutamide Resistance in Prostate Cancer. Curr. Mol. Biol. Rep. 2017, 3, 230–235. [CrossRef] [PubMed]

7. Giacinti, S.; Bassanelli, M.; Aschelter, A.M.; Milano, A.; Roberto, M.; Marchetti, P. Resistance to abiraterone in castration-resistant prostate cancer: A review of the literature. Anticancer Res. 2014, 34, 6265–6269. [PubMed]

8. Rice, M.A.; Malhotra, S.V.; Stoyanova, T. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. Front. Oncol. 2019, 9, 801. [CrossRef]

9. Perlmutter, M.A.; Lepor, H. Androgen Deprivation Therapy in the Treatment of Advanced Prostate Cancer. Rev. Urol. 2007, 9, S3–S8. [CrossRef] [PubMed]

10. Mostaghel, E.A. Abiraterone in the treatment of metastatic castration-resistant prostate cancer. Cancer Manag. Res. 2014, 6, 39–51. [CrossRef] [PubMed]

11. Carver, B.S.; Chapinski, C.; Wongvipat, J.; Hieronymus, H.; Chan, Y.; Chandarlapaty, S.; Arora, V.K.; Le, C.; Koutcher, J.; Scher, H.; et al. Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer. Cancer Cell 2011, 19, 575–586. [CrossRef] [PubMed]

12. Crumbaker, M.; Khoja, L.; Joshua, A.M. AR Signaling and the PI3K Pathway in Prostate Cancer. Cancers 2017, 9, 34. [CrossRef] [PubMed]

13. Pearson, H.; Li, J.; Méniel, V.; Fennell, C.; Waring, P.; Montgomery, K.G.; Rebello, R.J.; MacPherson, A.A.; Koushyar, S.; Furic, L.; et al. Identification of Pik3ca Mutation as a Genetic Driver of Prostate Cancer That Cooperates with Pten Loss to Accelerate Progression and Castration-Resistant Growth. Cancer Discov. 2018, 8, 764–779. [CrossRef] [PubMed]

14. Bitting, R.L.; Armstrong, A.J. Targeting the PI3K/Akt/mTOR pathway in castration-resistant prostate cancer. Endocr. Relat. Cancer 2013, 20, R83–R99. [CrossRef] [PubMed]

15. Hsieh, A.C.; Edlind, M.P. PI3K-AKT-mTOR signaling in prostate cancer progression and androgen deprivation therapy resistance. Asian J. Androl. 2014, 16, 378–386. [CrossRef] [PubMed]

16. Toren, P.; Zoubeidi, A. Targeting the PI3K/Akt pathway in prostate cancer: Challenges and opportunities (Review). Int. J. Onkol. 2014, 45, 1793–1801. [CrossRef]

17. Yang, J.; Nie, J.; Ma, X.; Wei, Y.; Peng, Y.; Wei, X. Targeting PI3K in cancer: Mechanisms and advances in clinical trials. Mol. Cancer 2019, 18, 26. [CrossRef]

18. Courtney, K.D.; Corcoran, R.B.; Engelman, J.A. The PI3K Pathway as Drug Target in Human Cancer. J. Clin. Oncol. 2010, 28, 1075–1083. [CrossRef]

19. Vanhaesebroeck, B.; Guillermet-Guibert, J.; Graupera, M.; Bilanges, B. The emerging mechanisms of isoform-specific PI3K signalling. Nat. Rev. Mol. Cell Biol. 2010, 11, 329–341. [CrossRef]

20. Thorpe, L.; Yuzugullu, H.; Zhao, J.J. PI3K in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. Nat. Rev. Cancer 2014, 15, 7–24. [CrossRef]

21. Liu, P.; Cheng, H.; Roberts, T.M.; Zhao, J.J. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat. Rev. Drug Discov. 2009, 8, 627–644. [CrossRef] [PubMed]

22. Guillermet-Guibert, J.; Bjorklof, K.; Salpekar, A.; Gonella, C.; Ramadani, F.; Bilancio, A.; Meek, S.; Smith, A.J.H.; Okkenhaug, K.; Vanhaesebroeck, B. The p110β isoform of phosphoinositide 3-kinase signal downstream of G protein-coupled receptors and is functionally redundant with p110γ. Proc. Natl. Acad. Sci. USA 2008, 105, 8292–8297. [CrossRef] [PubMed]

23. Papa, A.; Pandolfi, P.P. The PTEN-PI3K Axis in Cancer. Biomolecules 2019, 9, 153. [CrossRef] [PubMed]

24. Mulholland, D.J.; Tran, L.M.; Li, Y.; Cai, H.; Morim, A.; Wang, S.; Plaisier, S.; Garraway, L.P.; Huang, J.; Graeber, T.G.; et al. Cell Autonomous Role of PTEN in Regulating Castration-Resistant Prostate Cancer Growth. Cancer Cell 2011, 19, 792–804. [CrossRef]

25. Mendoza, M.C.; Er, E.E.; Blenis, J. The Ras-ERK and PI3K-mTOR pathways: Cross-talk and compensation. Trends Biochem. Sci. 2011, 36, 320–326. [CrossRef]
26. Gagliardi, P.A.; Puliafito, A.; Primo, L. PDK1: At the crossroad of cancer signaling pathways. *Semin. Cancer Biol.* 2018, 48, 27–35. [CrossRef]

27. Manning, B.D.; Toker, A. AKT/PKB Signaling: Navigating the Network. *Cell* 2017, 169, 381–405. [CrossRef]

28. Berenjeno, I.M.; Piñeiro, R.; Castillo, S.D.; Pearce, W.; McGranahan, N.; Dewhurst, S.M.; Meniel, V.; Birkbak, N.J.; Lau, E.; Sansregret, L.; et al. Oncogenic PIK3CA induces centrosome amplification and tolerance to genome doubling. *Nat. Commun.* 2017, 8, 1773. [CrossRef]

29. Huang, J.; Manning, B.D. A complex interplay between Akt, TSC2 and the two mTOR complexes. *Biochem. Soc. Trans.* 2009, 37, 217–222. [CrossRef]

30. Julien, L.-A.; Carri, A.; Moreau, J.; Roux, P.P. mTORC1-Activated S6K1 Phosphorylates Rictor on Threonine 1135 and Regulates mTORC2 Signaling. *Mol. Cell. Biol.* 2009, 30, 908–921. [CrossRef]

31. Cantley, L.C.; Wajant, H. The Phosphoinositide 3-Kinase Pathway. *Science* 2002, 296, 1655–1657. [CrossRef] [PubMed]

32. Sarbassov, D.D.; Guertin, D.A.; Ali, S.M.; Sabatini, D.M. Phosphorylation and Regulation of Akt/PKB by the Rictor-mTOR Complex. *Science* 2005, 307, 1098–1101. [CrossRef] [PubMed]

33. Mahajan, K.; Mahajan, N.P. PI3K-independent AKT activation in cancers: A treasure trove for novel therapeutics. *J. Cell. Physiol.* 2012, 227, 3178–3184. [CrossRef] [PubMed]

34. Faes, S.; Faes, O.D.S. PI3K and AKT: Unfaithful Partners in Cancer. *Cancer Cell* 2015, 28, 598–600. [CrossRef] [PubMed]

35. Liao, Y.; Grobholz, R.; Abel, U.; Trojan, L.; Michel, M.S.; Angel, P.; Mayer, D. Increase of AKT expression during the development of prostate cancer. *Prostate* 2006, 66, 1203–1212. [CrossRef]

36. Jewell, J.L.; Russell, R.C.; Guan, K.-L. Amino acid signalling upstream of mTOR. *Nat. Rev. Mol. Cell Biol.* 2013, 14, 133–139. [CrossRef]

37. Malik, S.N.; Brattain, M.; Ghosh, P.M.; Troyer, D.A.; Prihoda, T.; Bedolla, R.; Kreisberg, J.I. Immunohistochemical demonstration of phospho-Akt in high Gleason grade prostate cancer. *Clin. Cancer Res.* 2002, 8, 1168–1171.

38. Kremer, C.L.; Klein, R.R.; Mendelson, J.; Browne, W.; Samadzedeh, L.K.; Vanpatten, K.; Highstrom, L.; Pestano, G.A.; Nagle, R. Expression of mTOR signaling pathway markers in prostate cancer progression. *Prostate* 2006, 66, 1203–1212. [CrossRef]

39. Sutherland, S.I.; Benito, R.P.; Henshall, S.M.; Kench, J.G. Expression of phosphorylated-mTOR during the development of prostate cancer. *Prostate* 2014, 74, 1231–1239. [CrossRef]

40. Liao, Y.; Grobholz, R.; Abel, U.; Trojan, L.; Michel, M.S.; Angel, P.; Mayer, D. Increase of AKT/PKB expression correlates with gleason pattern in human prostate cancer. *Int. J. Cancer* 2003, 107, 676–680. [CrossRef]

41. Evren, S.; Dermen, A.; Lockwood, G.; Fleshner, N.; Sweet, J. mTOR–RAPTOR and 14-3-3? immunohistochemical expression in high grade prostatic intraepithelial neoplasia and prostatic adenocarcinomas: A tissue microarray study. *J. Clin. Pathol.* 2011, 64, 683–688. [CrossRef]

42. Grasso, C.S.; Wu, Y.-M.; Robinson, D.R.; Cao, X.; Dhanasekaran, S.M.; Khan, A.P.; Quist, M.J.; Jing, X.; Lonigro, R.J.; Brenner, J.C.; et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* 2012, 487, 239–243. [CrossRef] [PubMed]

43. Taylor, B.S.; Schultz, N.; Hieronymus, H.; Gopalan, A.; Xiao, Y.; Carver, B.S.; Arora, V.K.; Kaushik, P.; Cerami, E.; Reva, B.; et al. Integrative Genomic Profiling of Human Prostate Cancer. *Cancer Cell* 2010, 18, 11–22. [CrossRef] [PubMed]

44. Robinson, D.; Van Allen, E.M.; Wu, Y.-M.; Schultz, N.; Lonigro, R.J.; Mosquera, J.-M.; Montgomery, B.; Taplin, M.-E.; Pritchard, C.C.; Attard, G.; et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015, 161, 1215–1228. [CrossRef] [PubMed]

45. Armenia, J.; Wankowicz, S.A.M.; Liu, D.; Gao, J.; Kundra, R.; Reznik, E.; Chatila, W.K.; Chakravarty, D.; Han, G.C.; Coleman, I.; et al. The long tail of oncogenic drivers in prostate cancer. *Nat. Genet.* 2018, 50, 645–651. [CrossRef] [PubMed]

46. Abida, W.; Cytra, J.; Heller, G.; Prandi, D.; Armenia, J.; Coleman, I.; Benelli, M.; Robinson, D.; Van Allen, E.M.; et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc. Natl. Acad. Sci. USA* 2019, 116, 11428–11436. [CrossRef] [PubMed]

47. Cerami, E.; Gao, J.; Dogrusoz, U.; Gross, B.E.; Sumer, S.O.; Aksoy, B.A.; Skanderup, A.J.; Byrne, C.J.; Heuer, M.L.; Larsson, E.; et al. The cbio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012, 2, 401–404. [CrossRef]
48. Gao, J.; Aksoy, B.A.; Dogrusoz, U.; Dressner, G.; Gross, B.; Sumer, S.O.; Sun, Y.; Skanderup, A.J.; Sinha, R.; Larsson, E.; et al. Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. *Sci. Signal.* 2013, 6, p1. [CrossRef] [PubMed]

49. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* 2012, 490, 61–70. [CrossRef]

50. Kandoth, C.; Schultz, N.; Cherniack, A.D.; Akbani, R.; Liu, Y.; Shen, H.; Robertson, A.G.; Pashtan, I.; Shen, R.; Benz, C.C.; et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013, 497, 67–73. [CrossRef]

51. Lee, S.H.; Poulogiannis, G.; Pyne, S.; Jia, S.; Zou, L.; Signoretti, S.; Loda, M.; Cantley, L.C.; Roberts, T.M. A constitutively activated form of the p110β isoform of PI3-kinase induces prostatic intraepithelial neoplasia in mice. *Proc. Natl. Acad. Sci. USA* 2010, 107, 11002–11007. [CrossRef] [PubMed]

52. Schwartz, S.; Wongvipat, J.; Trigwell, C.B.; Hancox, U.; Carver, B.S.; Outmezguine, V.R.;; Will, M.; Yellen, P.; De Stanchina, E.; Baselga, J.; et al. Feedback suppression of PI3Kα signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3Kβ. *Cancer Cell* 2014, 27, 109–122. [CrossRef] [PubMed]

53. Jia, S.; Gao, X.; Lee, S.H.; Maira, S.-M.; Wu, X.; Stack, E.C.; Signoretti, S.; Loda, M.; Zhao, J.J.; Roberts, T.M. Opposing effects of androgen deprivation and targeted therapy on prostate cancer prevention. *Cancer Discov.* 2012, 3, 44–51. [CrossRef] [PubMed]

54. V anhaesebroeck, B.; Welham, M.J.; Kotani, K.; Stein, R.C.; Warne, P.H.; Zvelebil, M.; Higashi, K.; Volinia, S.; Downward, J.; Waterfield, M.D. p110δ, a novel phosphoinositide 3-kinase in leukocytes. *Proc. Natl. Acad. Sci. USA* 1997, 94, 4330–4335. [CrossRef]

55. Chantry, D.; Vojtek, A.; Kashishian, A.; Holtzman, D.A.; Wood, C.; Gray, P.W.; Cooper, J.A.; Hoekstra, M.F. p110δ, a Novel Phosphatidylinositol 3-Kinase Catalytic Subunit That Associates with p85 and Is Expressed Predominantly in Leukocytes. *J. Biol. Chem.* 1997, 272, 19236–19241. [CrossRef] [PubMed]

56. Eickholt, B.J.; Ahmed, A.; Davies, M.; Papakonstanti, E.; Pearce, W.; Starkey, M.L.; Zvelebil, M.; Higashi, K.; Volinia, S.; Smith, A.J.H.; Hall, S.M.; et al. Control of Axonal Growth and Regeneration of Sensory Neurons by the PI3Kδ isoform of PI3-kinase. *PLoS ONE* 2007, 2, e869. [CrossRef]

57. Tzenaki, N.; Papakonstanti, E. p110δ PI3 kinase pathway: Emerging roles in cancer. *Front. Oncol.* 2013, 3, 3. [CrossRef]

58. Tzenaki, N.; Andreou, M.; Stratigi, K.; Vergetaki, A.; Makrigiannakis, A.; Vanhaesebroeck, B.; Papakonstanti, E. High levels of p110δ PI3K expression in solid tumor cells suppress PTEN activity, generating cellular sensitivity to p110δ inhibitors through PTEN activation. *FASEB J.* 2012, 26, 2498–2508. [CrossRef]

59. Zehir, A.; Benayed, R.; Shah, R.; Syed, A.; Middha, S.; Kim, H.; Srinivasan, P.; Gao, J.; Chakravarty, D.; Devlin, S.M.; et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat. Med.* 2017, 23, 703–713. [CrossRef]

60. Wang, B.-D.; Ceniccola, K.; Hwang, S.; Andrawis, R.; Horvath, A.; Freedman, J.A.; Olender, J.; Knapp, S.; Ching, T.; Garmire, L.; et al. Alternative splicing promotes tumour aggressiveness and drug resistance in African American prostate cancer. *Nat. Commun.* 2017, 8, 15921. [CrossRef] [PubMed]

61. Ueki, K.; Yballe, C.M.; Brachmann, S.M.; Vicent, D.; Watt, J.M.; Kahn, C.R.; Cantley, L.C. Increased insulin sensitivity in mice lacking p85 subunit of phosphoinositide 3-kinase. *Proc. Natl. Acad. Sci. USA* 2001, 99, 419–424. [CrossRef] [PubMed]

62. Luo, J.; Field, S.J.; Lee, J.Y.; Engelmann, J.A.; Cantley, L.C. The p85 regulatory subunit of phosphoinositide 3-kinase down-regulates IRS-1 signaling via the formation of a sequestration complex. *J. Cell Biol.* 2005, 170, 455–464. [CrossRef]

63. Terauchi, Y.; Tsuji, Y.; Satoh, S.; Minoura, H.; Murakami, K.; Okuno, A.; Inukai, K.; Asano, T.; Kaburagi, Y.; Ueki, K.; et al. Increased insulin sensitivity and hypoglycaemia in mice lacking the p85α subunit of phosphoinositide 3-kinase. *Nat. Genet.* 1999, 21, 230–235. [CrossRef] [PubMed]

64. Mauvais-Jarvis, F.; Ueki, K.; Fruman, D.A.; Hirshman, M.F.; Sakamoto, K.; Goodyear, L.J.; Iannaccone, M.; Accili, M.; Cantley, L.C.; Kahn, C.R. Reduced expression of the murine p85α subunit of phosphoinositide 3-kinase improves insulin signaling and ameliorates diabetes. *J. Clin. Invest.* 2002, 109, 141–149. [CrossRef] [PubMed]
65. Taniguchi, C.M.; Winnay, J.; Kondo, T.; Bronson, R.T.; Guimaraes, A.R.; Aleman, J.O.; Luo, J.; Stephanopoulos, G.; Weissleder, R.; Cantley, L.C.; et al. The phosphoinositide 3-kinase regulatory subunit p85alpha can exert tumor suppressor properties through negative regulation of growth factor signaling. Cancer Res. 2010, 70, 5305–5315. [CrossRef] [PubMed]

66. Thorpe, L.M.; Spangle, J.M.; Ohlson, C.E.; Cheng, H.; Roberts, T.M.; Cantley, L.C.; Zhao, J.J. PI3K-p110alpha mediates the oncogenic activity induced by loss of the novel tumor suppressor PI3K-p85alpha. Proc. Natl. Acad. Sci. U.S.A. 2017, 114, 7095–7100. [CrossRef] [PubMed]

67. Philp, A.J.; Campbell, I.G.; Leet, C.; Vincan, E.; Rockman, S.P.; Whitehead, R.H.; Thomas, R.J.; Phillips, W.A. The phosphatidylinositol 3'-kinase p85alpha gene is an oncogene in human ovarian and colon tumors. Cancer Res. 2001, 61, 7426–7429. [PubMed]

68. Vallejo-Diaz, J.; Chagoyen, M.; Alazabal-Morán, M.; Gonzalez-Garcia, A.; Carrera, A. The Opposing Roles of PIK3R1/p85α and PIK3R2/p85β in Cancer. Trends Cancer 2019, 5, 233–244. [CrossRef]

69. Vallejo-Diaz, J.; Alazabal-Morán, M.; Cariaga-Martinez, A.E.; Pajares, M.J.; Flores, J.M.; Pio, R.; Montuenga, L.M.; Carrera, A. Targeted depletion of PIK3R2 induces regression of lung squamous cell carcinoma. Oncotarget 2016, 7, 85063–85078. [CrossRef]

70. Zhang, L.; Huang, J.; Yang, N.; Greshock, J.; Liang, S.; Hasegawa, K.; Giannakakis, A.; Poulos, N.; O’Brien-Jenkins, A.; Katsaros, D.; et al. Integrative genomic analysis of phosphatidylinositol 3'-kinase family identifies PIK3R3 as a potential therapeutic target in epithelial ovarian cancer. Clin. Cancer Res. 2007, 13, 5314–5321. [CrossRef]

71. Peng, Y.-P.; Zhu, Y.; Yin, L.-D.; Wei, J.-S.; Liu, X.-C.; Zhu, X.-L.; Miao, Y. PIK3R3 Promotes Metastasis of Pancreatic Cancer via ZEB1 Induced Epithelial-Mesenchymal Transition. Cell. Physiol. Biochem. 2018, 46, 1930–1938. [CrossRef] [PubMed]

72. Munkley, J.; Livermore, K.; McClurgg, U.L.; Kalna, G.; Knight, B.; McCullagh, P.; McGrath, J.; Crudwell, M.; Leung, H.Y.; Robson, C.; et al. The PI3K regulatory subunit gene PIK3R1 is under direct control of androgens and repressed in prostate cancer cells. Oncogene 2015, 2, 755–764. [CrossRef] [PubMed]

73. Han, R.; Zhang, L.; Gan, W.; Fu, K.; Jiang, K.; Ding, J.; Wu, J.; Han, X.; Li, D. piRNA-DQ722010 contributes to prostate hyperplasia of the male offspring mice after the maternal exposed to microcrystin-leucine arginine. Prostate 2019, 79, 798–812. [CrossRef] [PubMed]

74. Song, L.; Xie, Y.; Yu, S.; Peng, F.; Peng, L. MicroRNA-126 inhibits proliferation and metastasis by targeting pik3r2 in prostate cancer. Mol. Med. Rep. 2015, 13, 1204–1210. [CrossRef] [PubMed]

75. Brazzatti, J.; Klingler-Hoffmann, M.; Haylock-Jacobs, S.; Harata-Lee, Y.; Niu, M.; Higgins, M.D.; Kochetkova, M.; Hoffmann, P.; McColl, S.R. Differential roles for the p101 and p84 regulatory subunits of PI3Kγy in tumor growth and metastasis. Oncogene 2011, 31, 2350–2361. [CrossRef]

76. Rodgers, K.; Hammerman, P.S.; Lawrence, M.S.; Voet, D.; Jing, R.; Cibulskis, K.; Sivachenko, A.; Stojanov, P.; McKenna, A.; Lander, E.S.; et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012, 489, 519–525. [CrossRef]

77. Bass, A.J.; Thorsson, V.; Shmulevich, I.; Reynolds, S.M.; Miller, M.; Bernard, B.; Hinoue, T.; Laird, P.W.; Curtis, C.; Shen, H.; et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014, 513, 202–209. [CrossRef]

78. Akhani, R.; Akdemir, K.C.; Aksoy, B.A.; Albert, M.; Ally, A.; Amin, S.; Arachchi, H.; Arora, A.; Auman, J.T.; Ayalà, B.; et al. Genomic Classification of Cutaneous Melanoma. Cell 2015, 161, 1681–1696. [CrossRef]

79. Hoadley, K.A.; Yau, C.; Hinoue, T.; Wolf, D.M.; Lazar, A.J.F.; Drill, E.; Shen, R.; Taylor, A.M.; Cherniack, A.D.; Thorsson, V.; et al. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. Cell 2018, 173, 291–304.e6. [CrossRef]

80. Falasca, M.; Maffucci, T. Regulation and cellular functions of class II phosphoinositide 3-kinases. Biochim. J. 2012, 443, 587–601. [CrossRef]

81. Mavrommati, I.; Cisse, O.; Falasca, M.; Maffucci, T. Novel roles for class II Phosphoinositide 3-Kinase C2β in signalling pathways involved in prostate cancer cell invasion. Sci. Rep. 2016, 6, 23277. [CrossRef] [PubMed]

82. Raiborg, C.; Schink, K.O.; Stenmark, H.A. Class III phosphatidylinositol 3-kinase and its catalytic product PtdIns3P in regulation of endocytic membrane traffic. FEBS J. 2013, 280, 2730–2742. [CrossRef] [PubMed]

83. Backer, J.M. The intricate regulation and complex functions of the Class III phosphoinositide 3-kinase Vps34. Biochem. J. 2016, 473, 2251–2271. [CrossRef] [PubMed]
84. Bilanges, B.; Alliouache, S.; Pearce, W.; Morelli, D.; Szabadkai, G.; Chung, Y.-L.; Chicanne, G.; Valet, C.; Hill, J.M.; Voshol, P.J.; et al. Vps34 PI 3-kinase inactivation enhances insulin sensitivity through reprogramming of mitochondrial metabolism. *Nat. Commun.* 2017, 8, 1804. [CrossRef] [PubMed]

85. Simonsen, A.; Tooez, S.A. Coordination of membrane events during autophagy by multiple class III PI3-kinase complexes. *J. Cell Biol.* 2009, 186, 773–782. [CrossRef] [PubMed]

86. Nobukuni, T.; Joaquin, M.; Roccio, M.; Dann, S.G.; Kim, S.Y.; Byfield, M.P.; Backer, J.M.; Natt, F.; Bos, J.L.; et al. Amino acids mediate mTOR/raptor signaling through activation of class 3 phosphatidylinositol 3OH-kinase. *Proc. Natl. Acad. Sci. USA* 2005, 102, 14232–14237. [CrossRef]

87. Nezis, I.P.; Sagona, A.P.; Schink, K.O.; Stenmark, H. Divide and ProsPer: The emerging role of PtdIns3P in cytokinesis. *Trends Cell Biol.* 2010, 20, 642–649. [CrossRef]

88. Yoon, M.-S.; Son, K.; Arauz, E.; Han, J.M.; Kim, S.; Chen, J. Leucyl-tRNA Synthetase Activates Vps34 in Paraptosis. *Int. J. Mol. Sci.* 2018, 20, 4997–5000. [CrossRef]

89. Backer, J.M. The regulation and function of Class III PI3Ks: Novel roles for Vps34. *Biochem. J.* 2008, 410, 1–17. [CrossRef]

90. Dyson, J.M.; Fedele, C.G.; Davies, E.M.; Becanovic, J.; Mitchell, C.A. Phosphoinositide Phosphatases: Just as Important as the Kinases. *Subcell. Biochem.* 2012, 58, 215–279. [CrossRef]

91. Rudge, S.A.; Wakelam, M.J. Phosphatidylinositolphosphate phosphatase activities and cancer. *J. Lipid Res.* 2015, 57, 176–192. [CrossRef] [PubMed]

92. 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]

93. Cairns, P.; Okami, K.; Halachmi, S.; Halachmi, N.; Esteller, M.; Herman, J.G.; Jen, J.; Isaacs, W.B.; Bova, G.S.; Sidransky, D. Frequent inactivation of PTEN/MMAC1 in primary prostate cancer. *Cancer Res.* 1997, 57, 4997–5000. [PubMed]

94. Suzuki, H.; Freije, D.; Nusskern, D.R.; Okami, K.; Cairns, P.; Sidransky, D.; Isaacs, W.B.; Bova, G.S. Interfocal heterogeneity of PTEN/MMAC1 gene alterations in multiple metastatic prostate cancer tissues. *Cancer Res.* 1998, 58, 204–209. [PubMed]

95. Wang, S.I.; Parsons, R.; Ittmann, M. Homozygous deletion of the PTEN tumor suppressor gene in a subset of prostate adenocarcinomas. *Clin. Cancer Res.* 2004, 10, 811–815. [PubMed]

96. Maehama, T.; Dixon, J.E. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J. Biol. Chem.* 1998, 273, 13375–13378. [CrossRef] [PubMed]

97. Myers, M.P.; Stolarov, J.P.; Eng, C.; Li, J.; Wang, S.I.; Wigler, M.; Parsons, R.; Tonks, N.K. P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase. *Proc. Natl. Acad. Sci. USA* 1997, 94, 9052–9057. [CrossRef]

98. Geybels, M.S.; Fang, M.; Wright, J.L.; Qu, X.; Bibikova, M.; Klotzle, B.; Fan, J.-B.; Feng, Z.; Ostrander, E.A.; Nelson, P.S.; et al. PTEN loss is associated with prostate cancer recurrence and alterations in tumor DNA methylation profiles. *Oncotarget* 2017, 8, 84338–84348. [CrossRef]

99. McMenamin, M.E.; Soung, P.; Perera, S.; Kaplan, I.; Loda, M.; Sellers, W.R. Loss of PTEN expression in paraffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage. *Cancer Res.* 2001, 59, 4291–4296. [CrossRef]

100. Ratnacaram, C.K.; Telentin, M.; Jiang, M.; Meng, X.; Chambon, P.; Metzger, D. Temporally controlled ablation of PTEN in adult mouse prostate epithelium generates a model of invasive prostatic adenocarcinoma. *Proc. Natl. Acad. Sci. USA* 2008, 105, 2521–2526. [CrossRef]

101. Mulholland, D.J.; Kobayashi, N.; Russett, M.; Zhi, A.; Tran, L.M.; Huang, J.; Gleave, M.; Wu, H. Pten loss and RAS/MEK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. *Cancer Res.* 2012, 72, 1878–1889. [CrossRef] [PubMed]

102. Wang, S.; Gao, J.; Lei, Q.-Y.; Rozengurt, N.; Pritchard, C.; Jiao, J.; Thomas, G.V.; Li, G.; Roy-Burman, P.; Nelson, P.S.; et al. Prostate-specific deletion of the murine Pten tumor suppressor gene leads to metastatic prostate cancer. *Cancer Cell* 2003, 4, 209–221. [CrossRef]

103. Chen, Z.; Trotman, L.C.; Shaffer, D.; Lin, H.-K.; Dotan, Z.A.; Niki, M.; Koutcher, J.A.; Scher, H.I.; Ludwig, T.; Gerald, W.; et al. Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. *Nature* 2005, 436, 725–730. [CrossRef] [PubMed]
104. Ahmad, I.; Patel, R.; Singh, L.B.; Nixon, C.; Seywright, M.; Barnetson, R.J.; Brunton, V.G.; Muller, W.J.; Edwards, J.; Sansom, O.J.; et al. HER2 overcomes PTEN (loss)-induced senescence to cause aggressive prostate cancer. Proc. Natl. Acad. Sci. USA 2011, 108, 16392–16397. [CrossRef]

105. Kwak, M.K.; Johnson, D.T.; Zhu, C.; Lee, S.H.; Ye, D.-W.; Luong, R.; Sun, Z. Conditional Deletion of the Pten Gene in the Mouse Prostate Induces Prostatic Intraepithelial Neoplasms at Early Ages but a Slow Progression to Prostate Tumors. PLoS ONE 2013, 8, e53476. [CrossRef]

106. Trotman, L.C.; Niki, M.; Dotan, Z.A.; Koutcher, J.A.; Di Cristofano, A.; Xiao, A.; Khoo, A.S.; Roy-Burman, P.; Greenberg, N.M.; Van Dyke, T.; et al. Pten Dose Dictates Cancer Progression in the Prostate. PLoS Biol. 2003, 1, e9. [CrossRef]

107. Manda, K.R.; Tripathi, P.; Hsi, A.C.; Ning, J.; Ruzinova, M.B.; Liapis, H.; Bailey, M.; Zhang, H.; Maher, C.A.; Hodgson, M.C.; Shao, L.-J.; Frolov, A.; Li, R.; Peterson, L.; Ayala, G.; Ittmann, M.M.; Weigel, N.L.; Agoulnik, I.U.; Chan, T.O.; Rittenhouse, S.E.; Tischlis, P.N. AKT1-Dependent Breast Cancer Growth and Metastasis. Cancer Cell 2015, 36, 222–235. [CrossRef]

108. Rynkiewicz, N.K.; Fedele, C.G.; Chiam, K.; Gupta, R.; Kench, J.G.; Ooms, L.M.; McLean, C.; Giles, G.G.; Chen, H.; Li, H.; Chen, Q. INPP4B overexpression suppresses migration, invasion and angiogenesis of human prostate cancer cells. Clin. Exp. Pharmacol. Physiol. 2017, 44, 700–708. [CrossRef]

109. Correia, N.C.; Girio, A.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

110. Ooms, L.M.; Binge, L.C.; Davies, E.M.; Rahman, P.; Conway, J.R.; Gurung, R.; Ferguson, D.T.; Papa, A.; Fedele, C.G.; Vieusseux, J.L.; et al. The Inositol Polyphosphate 5-Phosphatase PIPP Regulates AKT1-Dependent Breast Cancer Growth and Metastasis. Cancer Cell 2015, 28, 155–169. [CrossRef]

111. Rodgers, S.J.; Ferguson, D.T.; Mitchell, C.A.; Ooms, L.M. Regulation of PI3K effector signalling in cancer by the phosphoinositide phosphatases. Biosci. Rep. 2017, 37. [CrossRef] [PubMed]

112. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

113. Gewinner, C.; Wang, Z.C.; Richardson, A.; Teruya-Feldstein, J.; Etemadmoghadam, D.; Bowtell, D.D.; Barretina, J.; Lin, W.M.; Rameh, L.; Salmena, L.; et al. Evidence that Inositol Polyphosphate 4-Phosphatase Type II Is a Tumor Suppressor That Inhibits PI3K Signaling. Cancer Cell 2009, 16, 115–125. [CrossRef] [PubMed]

114. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

115. Kofuji, S.; Kimura, H.; Nakanishi, H.; Nanjo, H.; Takasuga, S.; Liu, H.; Eguchi, S.; Nakamura, R.; Itoh, R.; Ueno, N.; et al. INPP4B Is a PtdIns(3,4,5)P3 Phosphatase That Can Act as a Tumor Suppressor. Cancer Discov. 2015, 5, 730–739. [CrossRef] [PubMed]

116. Chew, C.L.; Lunardi, A.; Gulluni, F.; Ruan, D.T.; Chen, M.; Salmena, L.; Nishino, M.; Papa, A.; Ng, C.; Fung, J.; et al. In Vivo Role of INPP4B in Tumor and Metastasis Suppression through Regulation of PI3K-AKT Signaling at Endosomes. Cancer Discov. 2015, 5, 740–751. [CrossRef] [PubMed]

117. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

118. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

119. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

120. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]

121. Correia, N.C.; Antunes, I.; Martins, L.R.; Barata, J. The multiple layers of non-genetic regulation of PTEN tumour suppressor activity. Eur. J. Cancer 2014, 50, 216–225. [CrossRef]
122. Manning, B.D.; Cantley, L.C. AKT/PKB Signaling: Navigating Downstream. *Cell* 2007, 129, 1261–1274. [CrossRef] [PubMed]

123. Alessi, D.R.; Deak, M.; Casamayor, A.; Caudwell, F.B.; Morrice, N.; Norman, D.G.; Gaffney, P.; Reese, C.B.; MacDougall, C.N.; Harbison, D.; et al. 3-Phosphoinositide-dependent protein kinase-1 (PDK1): Structural and functional homology with the Drosophila DSTPK61 kinase. *Curr. Biol.* 1997, 7, 776–789. [CrossRef]

124. Burgereing, B.; Coffer, P.J. Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. *Nature* 1995, 376, 599–602. [CrossRef] [PubMed]

125. Andjelković, M.; Jakubowicz, T.; Cron, P.; Ming, X.F.; Han, J.W.; Hemmings, B.A. Activation and phosphorylation of a pleckstrin homology domain containing protein kinase (RAC-PK/PKB) promoted by serum and protein phosphatase inhibitors. *Proc. Natl. Acad. Sci. USA* 1996, 93, 5699–5704. [CrossRef]

126. Gao, T.; Furnari, F.; Newton, A.C. PHLPP: A Phosphatase that Directly Dephosphorylates Akt, Promotes Apoptosis, and Suppresses Tumor Growth. *Mol. Cell* 2005, 18, 13–24. [CrossRef]

127. Pereira, B.; Chin, S.-F.; Rueda, O.M.; Vollan, H.-K.M.; Provenzano, E.; Bardwell, H.A.; Pugh, M.; Jones, L.; Russell, R.; Sammut, S.-J.; et al. The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes. *Nat. Commun.* 2016, 7, 11479. [CrossRef]

128. Bleecker, F.E.; Felicioni, L.; Buttitta, F.; Lamba, S.; Cardone, L.; Rodolfo, M.; Scarpa, A.; Leenstra, S.; Frattini, M.; Barbareschi, M.; et al. AKT1E17K in human solid tumours. *Oncogene* 2008, 27, 5648–5650. [CrossRef]

129. Troxell, M.L. PIK3CA/AKTI Mutations in Breast Carcinoma: A Comprehensive Review of Experimental and Clinical Studies. *J. Clin. Exp. Pathol.* 2012, S1-002. [CrossRef]

130. Shukla, S.; MacLennan, G.T.; Hartman, U.J.; Fu, P.; Resnick, M.I.; Gupta, S. Activation of PI3K-Akt signaling pathway promotes prostate cancer cell invasion. *Int. J. Cancer* 2007, 121, 1424–1432. [CrossRef]

131. Majumder, P.K.; Yeh, J.J.; George, D.J.; Febo, P.G.; Kum, J.; Xue, Q.; Bikoff, R.; Ma, H.; Kantoff, P.W.; Golub, T.R.; et al. Prostate intraepithelial neoplasia induced by prostate restricted Akt activation: The MPALK model. *Proc. Natl. Acad. Sci. USA* 2003, 100, 7841–7846. [CrossRef] [PubMed]

132. Li, B.; Sun, A.; Youn, H.; Hong, Y.; Terranova, P.F.; Thrasher, J.; Xu, P.; Spencer, D. Conditional Akt activation promotes androgen-independent progression of prostate cancer. *Carcinogenesis* 2006, 28, 572–583. [CrossRef]

133. Chen, M.-L.; Xu, P.-Z.; Peng, X.-D.; Chen, W.S.; Guzman, G.; Yang, X.; Di Cristofano, A.; Pandolfo, P.P.; Hay, N. The deficiency of Akt1 is sufficient to suppress tumor development in Pten−/− mice. *Genome Res.* 2006, 20, 1569–1574. [CrossRef] [PubMed]

134. De Bono, J.S.; De Giorgi, U.; Rodrigues, D.N.; Massard, C.; Bracarda, S.; Font, A.; Arija, J.A.A.; Shih, K.C.; Radavoi, G.D.; Xu, N.; et al. Randomized Phase II Study of Akt Blockade with or without Ipatasertib in Abiraterone-Treated Patients with Metastatic Prostate Cancer with and without PTEN Loss. *Clin. Cancer Res.* 2019, 25, 928–936. [CrossRef] [PubMed]

135. Maurer, M.; Su, T.; Saal, L.H.; Koujak, S.; Hopkins, B.D.; Barkley, C.R.; Wu, J.; Nandula, S.; Dutta, B.; Xie, Y.; et al. 3-Phosphoinositide-dependent kinase 1 potentiates upstream lesions on the phosphatidylinositol 3-kinase pathway in breast carcinoma. *Cancer Res.* 2009, 69, 6299–6306. [CrossRef] [PubMed]

136. Ellwood-Yen, K.; Keilhack, H.; Kunii, K.; Dolinski, B.; Connor, Y.; Hu, K.; Nagashima, K.; O’Hare, E.; Erkul, Y.; Di Bacco, A.; et al. PDK1 Attenuation Fails to Prevent Tumor Formation in PTEN-Deficient Transgenic Mouse Models. *Cancer Res.* 2011, 71, 3052–3065. [CrossRef]

137. Magee, J.A.; Chang, L.W.; Stormo, G.D.; Milbrandt, J. Direct, Androgen Receptor-Mediated Regulation of the FKBP5 Gene via a Distal Enhancer Element. *Endocrinology* 2006, 147, 590–598. [CrossRef]

138. Chen, M.; Pratt, C.; Zeeman, M.E.; Schultz, N.; Taylor, B.S.; O’Neill, A.; Castillo-Martin, M.; Nowak, D.G.; Naguib, A.; Grace, D.M.; et al. Identification of PHLPP1 as a Tumor Suppressor Reveals the Role of Feedback Activation in PTEN-Mutant Prostate Cancer Progression. *Cancer Cell* 2011, 20, 173–186. [CrossRef]

139. Nowak, D.G.; Katsenelson, K.C.; Wattrud, K.E.; Chen, M.; Mathew, G.; D’Andrea, V.D.; Lee, M.F.; Swamyathan, M.M.; Casanova-Salas, I.; Jibilian, M.C.; et al. The PHLPP2 phosphatase is a druggable driver of prostate cancer progression. *J. Cell Biol.* 2019, 218, 1943–1957. [CrossRef] [PubMed]

140. Pandey, P.; Seshacharyulu, P.; Das, S.; Rachagani, S.; Ponnusamy, M.P.; Yan, Y.; Johansson, S.L.; Datta, K.; Lin, M.F.; Batra, S.K. Impaired expression of protein phosphatase 2A subunits enhances metastatic potential of human prostate cancer cells through activation of AKT pathway. *Br. J. Cancer* 2013, 108, 2590–2600. [CrossRef]
141. Malik, N.; Macartney, T.; Hornberger, A.; Anderson, K.E.; Tovell, H.; Prescott, A.R.; Alessi, D.R. Mechanism of activation of SGK3 by growth factors via the Class 1 and Class 3 PI3Ks. *Biochem. J.* 2018, 475, 117–135. [CrossRef] [PubMed]

142. Basnet, R.; Gong, G.; Li, C.; Wang, M. Serum and glucocorticoid inducible protein kinases (SGKs): A potential target for cancer intervention. *Acta Pharm. Sin. B* 2018, 8, 767–771. [CrossRef] [PubMed]

143. Kobayashi, T.; Deak, M.; Morrice, N.; Cohen, P. Characterization of the structure and regulation of two novel isoforms of serum- and glucocorticoid-induced protein kinase. *Biochem. J.* 1999, 344, 189–197. [CrossRef] [PubMed]

144. Tessier, M.; Woodgett, J.R. Serum and glucocorticoid-regulated protein kinases: Variations on a theme. *J. Cell. Biochem.* 2006, 98, 1391–1407. [PubMed]

145. Castel, P.; Ellis, H.; Bago, R.; Toska, E.; Razavi, P.; Carmona, F.J.; Kannan, S.; Verma, C.S.; Dickler, M.; Chandra, S.; et al. PDK1-SGK1 Signaling Sustains AKT-Independent mTORC1 Activation and Confers Resistance to PI3Kα Inhibition. *Cancer Cell* 2016, 30, 229–242. [CrossRef]

146. Chou, M.M.; Hou, W.; Johnson, J.; Graham, L.K.; Lee, M.H.; Chen, C.S.; Newton, A.C.; Schaffhausen, B.S.; Toker, A. Regulation of protein kinase C zeta by PI3-kinase and PDK-1. *Curr. Biol.* 1998, 8, 1069–1077. [CrossRef]

147. Mizuno, H.; Nishida, E. The ERK MAP kinase pathway mediates induction of SGK (serum- and glucocorticoid-inducible kinase) by growth factors. *Genes Cells* 2001, 6, 261–268. [CrossRef]

148. Bago, R.; Sommer, E.; Castel, P.; Crafter, C.; Bailey, F.P.; Shpiro, N.; Baselga, J.; Cross, D.; Eyers, P.A.; Alessi, D.R. The hVps34- SGK 3 pathway alleviates sustained PI3K/Akt inhibition by stimulating mTORC 1 and tumour growth. *EMBO J.* 2016, 35, 1902–1922. [CrossRef]

149. Hayashi, M.; Tapping, R.I.; Chao, T.-H.; Lo, J.-F.; King, C.C.; Yang, Y.; Lee, J.-D. BMP1 Mediates Growth Factor-induced Cell Proliferation through Direct Cellular Activation of Serum and Glucocorticoid-inducible Kinase. *J. Biol. Chem.* 2001, 276, 8631–8634. [CrossRef]

150. Meng, F.; Yamagiwa, Y.; Taffetani, S.; Han, J.; Patel, T. IL-6 activates serum and glucocorticoid kinase via p38α mitogen-activated protein kinase pathway. *Am. J. Physiol. Physiol.* 2005, 289, C971–C981. [CrossRef]

151. Isikbay, M.; Otto, K.; Kregel, S.; Kach, J.; Cai, Y.; Griend, D.V.; Conzen, S.D.; Szmulewitz, R. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. *Horm. Cancer* 2014, 5, 72–89. [CrossRef] [PubMed]

152. Liu, W.; Wang, X.; Liu, Z.; Wang, Y.; Yin, B.; Yu, P.; Duan, X.; Liao, Z.; Chen, Y.; Liu, C.; et al. SGK1 inhibition induces autophagy-dependent apoptosis via the mTOR-Foxo3a pathway. *Br. J. Cancer* 2017, 117, 1139–1153. [CrossRef] [PubMed]

153. Gasser, J.A.; Inuzuka, H.; Lau, A.W.; Wei, W.; Beroukhim, R.; Toker, A. SGK3 mediates INPP4B-dependent PI3K signaling in breast cancer. *Mol. Cell* 2014, 56, 595–607. [CrossRef] [PubMed]

154. Bruhn, M.A.; Pearson, R.B.; Hannan, R.D.; Sheppard, K.E. Second AKT: The rise of SGK in cancer signalling. *Growth Factors* 2010, 28, 394–408. [CrossRef]

155. Chen, C.-C.; Jeon, S.-M.; Bhaskar, P.T.; Nogueira, V.; Sundararajan, D.; Tonic, I.; Park, Y.; Hay, N. FoxOs Inhibit mTORC1 and Activate Akt by Inducing the Expression of Sestrin3 and Rictor. *Dev. Cell* 2010, 18, 592–604. [CrossRef]

156. Zhang, Y.; Gan, B.; Liu, D.; Paik, J.-H. FoxO family members in cancer. *Cancer Biol. Ther.* 2011, 12, 253–259. [CrossRef]

157. Bach, D.-H.; Long, N.P.; Luu, E.-T.; Ahn, N.H.; Kwon, S.W.; Lee, S.K. The Dominant Role of Forkhead Box Proteins in Cancer. *Int. J. Mol. Sci.* 2018, 19, 3279. [CrossRef]

158. Van Der Heide, L.P.; Hoekman, M.F.M.; Smidt, M.P. The ins and outs of FoxO shuttling: Mechanisms of FoxO translocation and transcriptional regulation. *Biochem. J.* 2004, 380, 297–309. [CrossRef]

159. Hyytinen, E.-R.; Saadut, R.; Chen, C.; Paull, L.; Koiristo, P.A.; Vessella, R.L.; Frierson, H.F.; Dong, J.-T. Defining the region(s) of deletion at 6q16-q22 in human prostate cancer. *Genes Chromosom. Cancer* 2002, 34, 306–312. [CrossRef]

160. Ito, H.; Yoshida, K.; Ishii, K.; Suzuki, S.; Tabata, S.; Satoh, M.; Komatsu, M.; Ohsumi, Y. The hVps34- SGK 3 pathway alleviates sustained PI3K/Akt inhibition by stimulating mTORC 1 and tumour growth. *EMBO J.* 2016, 35, 1902–1922. [CrossRef]

161. Shukla, S.; Bhashkar, N.; MacLennan, G.T.; Gupta, S. Deregulation of FoxO3a accelerates prostate cancer progression in TRAMP mice. *Prostate* 2013, 73, 1507–1517. [CrossRef] [PubMed]
162. Yang, Y.; Blee, A.M.; Wang, D.; An, J.; Pan, Y.; Yan, Y.; Ma, T.; He, Y.; Dugdale, J.; Hou, X.; et al. Loss of FOXO1 Cooperates with TMPRSS2-ERG Overexpression to Promote Prostate Tumorigenesis and Cell Invasion. Cancer Res. 2017, 77, 6524–6537. [CrossRef] [PubMed]

163. Su, B.; Gao, L.; Baranowski, C.; Gillard, B.; Wang, J.; Ransom, R.; Ko, H.-K.; Gelman, L.H. A Genome-Wide RNAi Screen Identifies FOXO4 as a Metastasis-Suppressor through Counteracting PI3K/AKT Signal Pathway in Prostate Cancer. PLoS ONE 2014, 9, e101411. [CrossRef] [PubMed]

164. Dibble, C.; Elis, W.; Menon, S.; Qin, W.; Klekota, J.; Asara, J.M.; Finan, P.M.; Kwiatkowski, D.J.; Murphy, L.O.; Manning, B.D. TBC1D7 is a third subunit of the TSC1-TSC2 complex upstream of mTORC1. Mol. Cell 2012, 47, 535–546. [CrossRef] [PubMed]

165. Manning, B.D.; Tev, A.R.; Logsdon, M.N.; Blenis, J.; Cantley, L.C. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. Mol. Cell 2002, 10, 151–162. [CrossRef]

166. Inoki, K.; Zhu, T.; Guan, K.-L. TSC2 Mediates Cellular Energy Response to Control Cell Growth and Survival. Cell 2003, 115, 577–590. [CrossRef]

167. Inoki, K.; Ouyang, H.; Zhu, T.; Lindvall, C.; Wang, Y.; Zhang, X.; Yang, Q.; Bennett, C.; Harada, Y.; Stankunas, K.; et al. TSC2 Integrates Wnt and Energy Signals via a Coordinated Phosphorylation by AMPK and GSK3 to Regulate Cell Growth. Cell 2006, 126, 955–968. [CrossRef]

168. Shaw, R.J.; Bardeesy, N.; Manning, B.D.; Lopez, L.; Kosmatka, M.; DePinho, R.A.; Cantley, L.C. The LKB1 tumor suppressor negatively regulates mTOR signaling. Cancer Cell 2004, 6, 91–99. [CrossRef]

169. Liang, M.-C.; Ma, J.; Chen, L.; Kozlowski, P.; Qin, W.; Li, D.; Goto, J.; Shimamura, T.; Hayes, D.N.; Meyerson, M.; et al. TSC1 loss synergizes with KRAS activation in lung cancer development in the mouse and confers rapamycin sensitivity. Oncogene 2009, 29, 1588–1597. [CrossRef]

170. Ho, D.W.H.; Chan, L.K.; Chu, Y.T.; Xu, I.M.J.; Poon, R.T.P.; Cheung, T.T.; Tang, C.N.; Tang, V.W.L.; Lo, I.L.; Lam, P.W.Y.; et al. TSC1/2mutations define a molecular subset of HCC with aggressive behaviour and treatment implication. Gut 2016, 66, 1496–1506. [CrossRef]

171. Kladney, R.D.; Cardiff, R.D.; Kwiatkowski, D.J.; Chiang, G.G.; Weber, J.D.; Arbeid, J.M.; Lu, Z.H. Tuberous sclerosis complex 1: An epithelial tumor suppressor essential to prevent spontaneous prostate cancer in aged mice. Cancer Res. 2010, 70, 8937–8947. [CrossRef] [PubMed]

172. Ma, L.; Teruya-Feldstein, J.; Behrendt, N.; Chen, Z.; Noda, T.; Hino, O.; Cordon-Cardo, C.; Pandolfi, P.P. Genetic analysis of Pten and Tsc2 functional interactions in the mouse reveals asymmetrical haploinsufficiency in tumor suppression. Genes Dev. 2005, 19, 1779–1786. [CrossRef] [PubMed]

173. Sato, N.; Koinuma, J.; Ito, T.; Tsuchiya, E.; Kondo, S.; Nakamura, Y.; Daigo, Y. Activation of an oncogenic TBC1D7 (TBC1 domain family, member 7) protein in pulmonary carcinogenesis. Genes Chromosom. Cancer 2010, 49, 353–367. [CrossRef]

174. Thien, A.; Prentzell, M.T.; Holzwarth, B.; Kläsener, K.; Kuper, I.; Boehlke, C.; Sonntag, A.G.; Ruf, S.; Maerz, L.; Kladsney, R.D.; Cardiff, R.D.; Kwiatkowski, D.J.; Chiang, G.G.; Weber, J.D.; Arbeid, J.M.; Lu, Z.H. Tuberous sclerosis complex 1: An epithelial tumor suppressor essential to prevent spontaneous prostate cancer in aged mice. Cancer Res. 2010, 70, 8937–8947. [CrossRef] [PubMed]

175. Ma, L.; Teruya-Feldstein, J.; Behrendt, N.; Chen, Z.; Noda, T.; Hino, O.; Cordon-Cardo, C.; Pandolfi, P.P. Genetic analysis of Pten and Tsc2 functional interactions in the mouse reveals asymmetrical haploinsufficiency in tumor suppression. Genes Dev. 2005, 19, 1779–1786. [CrossRef] [PubMed]

176. Laplante, M.; Sabatini, D.M. mTOR Signaling in Growth Control and Disease. Cell 2012, 149, 274–293. [CrossRef] [PubMed]

177. Kim, L.C.; Cook, R.S.; Chen, J. mTORC1 and mTORC2 in cancer and the tumor microenvironment. Oncogene 2016, 35, 2965–2979. [CrossRef]

178. Conciatori, F.; Ciuffreda, L.; Bazzichetto, C.; Falcone, I.; Pilotto, S.; Bria, E.; Cognetti, F.; Milella, M. mTOR Cross-Talk in Cancer and Potential for Combination Therapy. Cancers 2018, 10, 23. [CrossRef] [PubMed]
181. Ma, X.M.; Blenis, J. Molecular mechanisms of mTOR-mediated translational control. Nat. Rev. Mol. Cell Biol. 2009, 10, 307–318. [CrossRef] [PubMed]

182. Fenton, T.R.; Gout, I. Functions and regulation of the 70 kDa ribosomal S6 kinases. Int. J. Biochem. Cell Biol. 2011, 43, 47–59. [CrossRef] [PubMed]

183. Meyuhas, O.; Dreazen, A. Chapter 3 Ribosomal Protein S6 Kinase. Prog. Mol. Biol. Transl. Sci. 2009, 90, 109–153. [CrossRef] [PubMed]

184. García-Martínez, J.M.; Alessi, D.R. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem. J. 2008, 416, 375–385. [CrossRef]

185. Sarbassov, S.D.; Ali, S.M.; Sengupta, S.; Sheen, J.-H.; Hsu, P.P.; Bagley, A.F.; Markhard, A.L.; Sabatini, D.M. Prolonged Rapamycin Treatment Inhibits mTORC2 Assembly and Akt/ PKB. Mol. Cell 2006, 22, 159–168. [CrossRef]

186. Jhanwar-Uniyal, M.; Wainwright, J.V.; Mohan, A.L.; Tobias, M.E.; Murali, R.; Gandhi, C.D.; Schmidt, M.H.; Jhanwar-Uniyal, M. Diverse signaling mechanisms of mTOR complexes: mTORC1 and mTORC2 in forming a formidable relationship. Adv. Biol. Regul. 2019, 72, 51–62. [CrossRef]

187. Peterson, T.R.; Laplante, M.; Thoreen, C.C.; Sancak, Y.; Kuehl, W.M.; Gray, N.S.; Sabatini, D.M. DEPTOR Is an mTOR Inhibitor Frequently Overexpressed in Multiple Myeloma Cells and Required for Their Survival. Cell 2009, 137, 873–886. [CrossRef]

188. Wang, Q.; Zhou, Y.; Rychahou, P.; Harris, J.W.; Zaytseva, Y.Y.; Liu, J.; Wang, C.; Weiss, H.; Liu, C.; Lee, E.Y.; et al. Deptor is a novel target of Wnt/β-catenin/c-Myc and contributes to colorectal cancer cell growth. Cancer Res. 2018, 78, 3163–3175. [CrossRef]

189. Catena, V.; Bruno, T.; De Nicola, F.; Goeman, F.; Pallocca, M.; Iezzi, S.; Sorino, C.; Cigliana, G.; Floridi, A.; Blandino, G.; et al. Depor transcriptionally regulates endoplasmic reticulum homeostasis in multiple myeloma cells. Oncotarget 2016, 7, 70546–70558. [CrossRef]

190. Guertin, D.A.; Stevens, D.M.; Saïto, M.; Kinkel, S.; Crosby, K.; Sheen, J.-H.; Mullholland, D.J.; Magnuson, M.A.; Wu, H.; Sabatini, D.M. mTOR Complex 2 Is Required for the Development of Prostate Cancer Induced by Pten Loss in Mice. Cancer Cell 2009, 15, 148–159. [CrossRef]

191. Demetriades, C.; Plescher, M.; Teleman, A.A. Lysosomal recruitment of TSC2 is a universal response to cellular stress. Nat. Commun. 2016, 7, 10662. [CrossRef] [PubMed]

192. Saxton, R.A.; Sabatini, D.M. mTOR Signaling in Growth, Metabolism, and Disease. Cell 2017, 168, 960–976. [CrossRef] [PubMed]

193. Sabatini, D.M. Twenty-five years of mTOR: Uncovering the link from nutrients to growth. Nat. Rev. Mol. Cell Biol. 2009, 10, 4728. [CrossRef]

194. Sabatini, D.M. Twenty-five years of mTOR: Uncovering the link from nutrients to growth. Nat. Rev. Mol. Cell Biol. 2009, 10, 4728. [CrossRef]

195. Nguyen, T.P.; Frank, A.R.; Jewell, J.L. Amino acid and small GTPase regulation of mTORC1. Cell. Logist. 2017, 7, e1378794. [CrossRef]

196. Jewell, J.L.; Kim, Y.C.; Russell, R.C.; Yu, F.-X.; Park, H.W.; Plouffe, S.W.; Tagliabracci, V.S.; Guan, K.-L. Differential regulation of mTORC1 by leucine and glutamine. Science 2015, 347, 194–198. [CrossRef]

197. Mihaylova, M.M.; Shaw, R.J. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nature 2011, 13, 1016–1023. [CrossRef]

198. Dasgupta, B.; Ju, J.-S.; Sasaki, Y.; Liu, X.; Jung, S.-R.; Higashida, K.; Lindquist, D.; Milbrandt, J. The AMPK β2 Subunit Is Required for Energy Homeostasis during Metabolic Stress. Mol. Cell. Biol. 2012, 32, 2837–2848. [CrossRef]

199. Gwinn, D.M.; Shackelford, D.B.; Egan, D.F.; Mihaylova, M.M.; Méry, A.; Vasquez, D.S.; Turk, B.E.; Shaw, R.J. AMPK Phosphorylation of Raptor Mediates a Metabolic Checkpoint. Mol. Cell 2008, 30, 214–226. [CrossRef]

200. Han, F.; Li, C.-F.; Cai, Z.; Zhang, X.; Jin, G.; Zhang, W.-N.; Xu, C.; Wang, C.-Y.; Morrow, J.; Zhang, S.; et al. The critical role of AMPK in driving Akt activation under stress, tumorigenesis and drug resistance. Nat. Commun. 2018, 9, 4728. [CrossRef]

201. Han, Y.; Hu, Z.; Cui, A.; Liu, Z.; Ma, F.; Xue, Y.; Liu, Y.; Zhang, F.; Zhao, Z.; Yu, Y.; et al. Post-translational regulation of lipogenesis via AMPK-dependent phosphorylation of insulin-induced gene. Nat. Commun. 2019, 10, 623. [CrossRef] [PubMed]
202. Choudhury, Y.; Yang, P.Z.; Ahmad, I.; Nixon, C.; Salt, I.P.; Leung, H.Y. AMP-activated protein kinase (AMPK) as a potential therapeutic target independent of PI3K/Akt signaling in prostate cancer. Oncoscience 2014, 1, 446. [CrossRef] [PubMed]

203. Hardie, D.G. Molecular Pathways: Is AMPK a Friend or a Foe in Cancer? Clin. Cancer Res. 2015, 21, 3836–3840. [CrossRef] [PubMed]

204. Abeshouse, A.; Ahn, J.; Akbani, R.; Ally, A.; Amin, S.; Andry, C.D.; Annala, M.; Aprikian, A.; Armenia, J.; Arora, A.; et al. The Molecular Taxonomy of Primary Prostate Cancer. Cell 2015, 163, 1011–1025. [CrossRef] [PubMed]

205. Zadra, G.; Photopoulos, C.; Tyekucheva, S.; Heidari, P.; Weng, Q.P.; Fedele, G.; Liu, H.; Scaglia, M.; Priolo, C.; Scaglia, N.; et al. A novel direct activator of AMPK inhibits prostate cancer growth by blocking lipogenesis. EMBO Mol. Med. 2014, 6, 519–538. [CrossRef] [PubMed]

206. Tennenkoon, J.B.; Shi, Y.; Han, J.J.; Tsouko, E.; White, M.A.; Burns, A.R.; Zhang, A.; Xia, X.; Ilkayeva, O.R.; Xin, L.; et al. Androgens regulate prostate cancer cell growth via an AMPK-PGC-1α-mediated metabolic switch. Oncogene 2013, 33, 5251–5261. [CrossRef] [PubMed]

207. Choudhury, Y.; Yang, P.Z.; Ahmad, I.; Nixon, C.; Salt, I.P.; Leung, H.Y. AMP-activated protein kinase (AMPK) as a potential therapeutic target independent of PI3K/Akt signaling in prostate cancer. Oncoscience 2014, 1, 446. [CrossRef] [PubMed]

208. Sanchez-Cespedes, M. The role of LKB1 in lung cancer. Fam. Cancer 2011, 10, 447–453. [CrossRef]

209. Hindi, S.M.; Sato, S.; Xiong, G.; Bohnert, K.R.; Gibb, A.A.; Gallot, Y.S.; McMillan, J.; Hill, B.G.; Uchida, S.; Kumar, A. TAK1 regulates skeletal muscle mass and mitochondrial function. JCI Insight 2018, 3. [CrossRef]

210. Penfold, L.; Woods, A.; Muckett, P.; Nikitin, A.Y.; Kent, T.R.; Zhang, S.; Graham, R.; Pollard, A.; Carling, D. CAMKK2 Promotes Prostate Cancer Independently of AMPK via Increased Lipogenesis. Cancer Res. 2018, 78, 6747–6761. [CrossRef]

211. Mehenni, H.; Lin-Marq, N.; Buchet-Poyau, K.; Reymond, A.; Collart, M.A.; Picard, D.; Antonarakis, S.E. LKB1 interacts with and phosphorylates PTEN: A functional link between two proteins involved in cancer predisposing syndromes. Hum. Mol. Genet. 2005, 14, 2209–2219. [CrossRef] [PubMed]

212. Shorning, B.Y.; Clarke, A. Energy sensing and cancer: LKB1 function and lessons learnt from Peutz-Jeghers syndrome. Semin. Cell Dev. Biol. 2016, 52, 21–29. [CrossRef]

213. Pearson, H.; McCarthy, A.; Collins, C.M.; Ashworth, S.; Clarke, A. Lkb1 Deficiency Causes Prostate Neoplasia in the Mouse. Cancer Res. 2008, 68, 2223–2232. [CrossRef] [PubMed]

214. Gocher, A.M.; Azabdaftari, G.; Euscher, L.M.; Dai, S.; Karacosta, L.G.; Franke, T.F.; Edelman, A.M. Akt activation by Ca²⁺/calmodulin-dependent protein kinase 2 (CaMKK2) in ovarian cancer cells. J. Biol. Chem. 2017, 292, 14188–14204. [CrossRef] [PubMed]

215. Mehenni, H.; Lin-Marq, N.; Buchet-Poyau, K.; Reymond, A.; Collart, M.A.; Picard, D.; Antonarakis, S.E. LKB1 interacts with and phosphorylates PTEN: A functional link between two proteins involved in cancer predisposing syndromes. Hum. Mol. Genet. 2005, 14, 2209–2219. [CrossRef] [PubMed]

216. Xu, P.; Cai, F.; Liu, X.; Guo, L. LKB1 suppresses proliferation and invasion of prostate cancer through hedgehog signaling pathway. Int. J. Clin. Exp. Pathol. 2014, 7, 8480–8488.

217. Budanov, A.; Karin, M. p53 Target Genes Sestrin1 and Sestrin2 Connect Genotoxic Stress and mTOR Signaling. Cell 2008, 134, 451–460. [CrossRef]

218. Morrison, A.; Chen, L.; Wang, J.; Zhang, M.; Yang, H.; Ma, Y.; Budanov, A.; Lee, J.H.; Karin, M.; Li, J. Sestrin2 promotes LKB1-mediated AMPK activation in the ischemic heart. FASEB J. 2014, 29, 408–417. [CrossRef]

219. Wang, M.; Xu, Y.; Liu, J.; Ye, J.; Yuan, W.; Jiang, H.; Wang, Z.; Jiang, H.; Wan, J. Recent Insights into the Biological Functions of Sestrins in Health and Disease. Cell. Physiol. Biochem. 2017, 43, 1731–1741. [CrossRef]

220. Parmigiani, A.; Nourbakhsh, A.; Ding, B.; Wang, W.; Kim, Y.C.; Akopiants, K.; Guan, K.-L.; Karin, M.; Budanov, A. Sestrins inhibit mTORC1 kinase activation through the GATOR complex. Cell Rep. 2014, 9, 1281–1291. [CrossRef]

221. Cordani, M.; Sanchez-Alvarez, M.; Strippoli, R.; Bazhin, A.; Donadelli, M. Sestrins at the Interface of ROS Control and Autophagy Regulation in Health and Disease. Oxidative Med. Cell. Longev. 2019, 2019, 1283075. [CrossRef] [PubMed]

222. Pasha, M.; Eid, A.; Eid, A.A.; Gorin, Y.; Munusamy, S. Sestrin2 as a Novel Biomarker and Therapeutic Target for Various Diseases. Oxidative Med. Cell. Longev. 2017, 2017, 1–10. [CrossRef] [PubMed]

223. Wang, G.; Jones, S.; Marra, M.A.; Sadar, M.D. Identification of genes targeted by the androgen and PKA signaling pathways in prostate cancer cells. Oncogene 2006, 25, 7311–7323. [CrossRef] [PubMed]
224. Mihaly, S.R.; Ninomiya-Tsuji, J.; Morioka, S. TAK1 control of cell death. Cell Death Differ. 2014, 21, 1667–1676. [CrossRef] [PubMed]

225. Cheng, J.-S.; Tsai, W.-L.; Liu, P.-F.; Goan, Y.-G.; Lin, C.-W.; Tseng, H.-H.; Lee, C.-H.; Shu, C.-W. The MAP3K7-mTOR Axis Promotes the Proliferation and Malignancy of Hepatocellular Carcinoma Cells. Front. Oncol. 2019, 9, 474. [CrossRef]

226. Kluth, M.; Hesse, J.; Heinl, A.; Krohn, A.; Steurer, S.; Sirma, H.; Simon, R.; Mayer, P.-S.; Schumacher, U.; Grupp, K.; et al. Genomic deletion of MAP3K7 at 6q12-22 is associated with early PSA recurrence in prostate cancer and absence of TP53R2-ERG fusions. Mod. Pathol. 2013, 26, 975–983. [CrossRef]

227. Wu, M.; Shi, L.; Cimic, A.; Romero, L.; Sui, G.; Lees, C.; Li, H.; Zhu, X. mTOR signaling pathway and mTOR inhibitors in cancer: Progress and challenges. Cell Biosci. 2020, 10, 1–11. [CrossRef]

228. Bosman, M.C.J.; Schepers, H.; Jaques, J.; Brouwers-Vos, A.Z.; Quax, W.J.; Schuringa, J.J.; Vellenga, E. The TAK1-NF-κB axis as therapeutic target for AML. Blood 2014, 124, 3130–3140. [CrossRef]

229. Janku, F.; Yap, T.A.; Meric-Bernstam, F. Targeting the PI3K pathway in cancer: Are we making headway? Nat. Rev. Clin. Oncol. 2018, 15, 273–291. [CrossRef]

230. Zou, Z.; Tao, T.; Li, H.; Zhu, X. mTOR signaling pathway and mTOR inhibitors in cancer: Progress and challenges. Cell Biosci. 2020, 10, 1–11. [CrossRef]

231. Sathe, A.; Chalaud, G.; Oppolzer, I.; Wong, K.Y.; Von Busch, M.; Schmid, S.C.; Tong, Z.; Retz, M.; Gschwend, J.E.; Schulz, W.A.; et al. Parallel PI3K, AKT and mTOR inhibition is required to control feedback loops that limit tumor therapy. PLoS ONE 2018, 13, e0190854. [CrossRef] [PubMed]

232. Rozengurt, E.; Soares, H.P.; Sinnet-Smith, J. Suppression of feedback loops mediated by PI3K/mTOR induces multikinase overactivation of compensatory pathways: An unintended consequence leading to drug resistance. Mol. Cancer Ther. 2006, 5, 1323–1333. [CrossRef] [PubMed]

233. Zhang, H.H.; Lipovsky, A.I.; Dibble, C.; Sahin, M.; Manning, B.D. S6K1 Regulates GSK3 under Conditions of mTOR-Dependent Feedback Inhibition of Akt. Mol. Cell. 2006, 24, 185–197. [CrossRef] [PubMed]

234. Rodrik-Outmezguine, V.S.; Chandarlapaty, S.; Pagano, N.C.; Poulikakos, P.I.; Scaltriti, M.; Moskatel, E.; Baselga, J.; Guichard, S.; Rosen, N. mTOR kinase inhibition causes feedback-dependent biphasic regulation of Akt signaling. Cancer Discov. 2011, 1, 248–259. [CrossRef] [PubMed]

235. O’Reilly, K.E.; Rojo, F.; She, Q.-B.; Solit, D.; Mills, G.B.; Smith, D.; Lane, H.; Hofmann, F.; Hicklin, D.J.; Ludwig, D.L.; et al. mTOR inhibition induces upstream receptor tyrosine kinase kinase signaling and activates Akt. Cancer Res. 2006, 66, 1500–1508. [CrossRef] [PubMed]

236. Margolis, B.; Skolnik, E.Y. Activation of Ras by receptor tyrosine kinases. J. Am. Soc. Nephrol. 1994, 5, 1288–1299.

237. Santarpia, L.; Lippman, S.M.; El-Naggar, A.K. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin. Ther. Targets 2012, 16, 103–119. [CrossRef]

238. Fernández-Medarde, A.; Santos, E. Ras in Cancer and Developmental Diseases. Genes Cancer 2011, 2, 344–358. [CrossRef]

239. Steelman, L.S.; Chappell, W.H.; Abrams, S.L.; Kempf, C.R.; Long, J.; Laidler, P.; Mijatović, S.; Maksimovic-Ivanic, D.; Stivala, F.; Mazzarino, M.C.; et al. Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging. Aging 2011, 3, 192–222. [CrossRef]

240. Copps, K.D.; White, M. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia 2012, 55, 2565–2582. [CrossRef] [PubMed]

241. Copps, K.D.; White, M. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia 2012, 55, 2565–2582. [CrossRef] [PubMed]

242. Dibble, C.; Asara, J.M.; Manning, B.D. Characterization of Rictor phosphorylation Sites Reveals Direct Regulation of mTOR Complex 2 by S6K1. Mol. Cell. Biol. 2009, 29, 5657–5670. [CrossRef] [PubMed]

243. Suire, S.; Hawkins, P.; Stephens, L. Activation of phosphoinositide 3-kinase gamma by Ras. Expert Opin. Ther. Targets 2006, 10, 1667–1676. [CrossRef]

244. Ma, L.; Chen, Z.; Erdjument-Bromage, H.; Tempest, P.; Pandolfi, P.P. Phosphorylation and Functional Inactivation of TSC2 by Erk. Cell 2005, 121, 179–193. [CrossRef]

245. Carrière, A.; Cargnello, M.; Julien, L.-A.; Gao, H.; Bonneil, É.; Thibault, P.; Roux, P.P. Oncogenic MAPK Signaling Stimulates mTORC1 Activity by Promoting RSK-Mediated Raptor Phosphorylation. Curr. Biol. 2008, 18, 1269–1277. [CrossRef]
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
CrossRef
PubMed
PubMed
PubMed

253. Wu, L.; Birle, D.C.; Tanner, I.F. E

246. Carriere, A.; Romeo, Y.; Acosta-Jaquez, H.A.; Moreau, J.; Bonneil, E.; Thibault, P.; Fingar, D.C.; Roux, P.P.
ERK1/2 Phosphorylate Raptor to Promote Ras-dependent Activation of mTOR Complex 1 (mTORC1). J. Biol.
Chem. 2011, 286, 567–577. [CrossRef]

247. Lara, R.; Seckl, M.J.; Pardo, O.E. The p90 RSK Family Members: Common Functions and Isoform Specificity.
Cancer Res. 2013, 73, 5301–5308. [CrossRef]

248. Roux, P.P.; Shahbazian, D.; Vu, H.; Holz, M.K.; Cohen, M.S.; Taunton, J.; Sonenberg, N.; Blenis, J.
RAS/ERK signaling promotes site-specific ribosomal protein S6 phosphorylation via RSK and stimulates cap-dependent
translation. J. Biol. Chem. 2007, 282, 14056–14064. [CrossRef]

249. Zimmermann, S. Phosphorylation and Regulation of Raf by Akt (Protein Kinase B). Science 1999, 286,
1741–1744. [CrossRef]

250. Guan, K.-L. Negative regulation of the serine/threonine kinase B-Raf by Akt. J. Biol. Chem. 2000, 275, 275.
[CrossRef]

251. Lone, M.-U.-D.; Miyan, J.; Asif, M.; Malik, S.A.; Dubey, P.; Singh, V.; Singh, K.; Mitra, K.; Pandey, D.; Haq, W.;
et al. Direct physical interaction of active Ras with mSIN1 regulates mTORC2 signaling. BMC Cancer 2019,
19, 1–16. [CrossRef] [PubMed]

252. Majumder, P.K.; Febbo, P.G.; Bikoff, R.; Berger, R.; Xue, Q.; McMahon, L.M.; Manola, J.; Brugarolas, J.;
McDonnell, T.J.; Golub, T.R.; et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia
through regulation of apoptotic and HIF-1-dependent pathways. Nat. Med. 2004, 10, 594–601. [CrossRef] [PubMed]

255. Carracedo, A.; Ma, L.; Teruya-Feldstein, J.; Rojo, F.; Salmona, L.; Alimonti, A.; Egia, A.; Sasaki, A.T.;
Amato, R.J.; Jac, J.; Mohammad, T.; Saxena, S. Pilot Study of Rapamycin in Patients with Hormone-Refractory
Prostate Cancer. Clin. Genitourin. Cancer 2013, 11, 1322–1326. [CrossRef]

258. Shi, Y.; Yan, H.; Frost, P.; Gera, J.; Lichtenstein, A. Mammalian target of Rapamycin Inhibitor CCI-779 Used Alone
or with Chemotherapy on Human Prostate Cancer Cells and Xenografts. Cancer Res. 2005, 65, 2825–2831.
[CrossRef] [PubMed]

259. Thomas, G.; Kozma, S.C.; et al. Inhibition of mTORC1 leads to MAPK pathway activation through a
phosphorylation promotes nuclear exclusion of the winged helix transcription factor FKHR1. Proc. Natl.
Acad. Sci. USA 1999, 96, 7421–7426. [CrossRef] [PubMed]
264. Brunet, A.; Bonni, A.; Zigmond, M.J.; Lin, M.Z.; Juo, P.; Hu, L.S.; Anderson, M.J.; Arden, K.C.; Blenis, J.; Greenberg, M.E. Akt Promotes Cell Survival by Phosphorylating and Inhibiting a Forkhead Transcription Factor. *Cell* 1999, 96, 857–868. [CrossRef]

265. Chakrabarty, A.; Sánchez, V.; Kuba, M.G.; Rinehart, C.; Arteaga, C.L. Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors. *Proc. Natl. Acad. Sci. USA* 2011, 109, 2718–2723. [CrossRef]

266. Serra, V.; Scaltriti, M.; Prudkin, L.; Eichhorn, P.J.A.; Ibrahim, Y.H.; Chandarlapaty, S.; Markman, B.; Rodriguez, O.; Guzmán, M.; Rodriguez, S.; et al. PI3K inhibition results in enhanced HER signaling and acquired ERK dependence in HER2-overexpressing breast cancer. *Oncogene* 2011, 30, 2547–2557. [CrossRef]

267. Sommer, E.M.; Dry, H.; Cross, D.; Guichard, S.; Davies, B.R.; Alessi, D.R. Elevated SGK1 predicts resistance of breast cancer cells to Akt inhibitors. *Biochem. J.* 2013, 452, 499–508. [CrossRef]

268. Wang, J.; Kobayashi, T.; Floc’h, N.; Kinkade, C.W.; Aytes, A.; Dankort, D.; Lefebvre, C.; Mitrofanova, A.; Cardiff, R.D.; McMahon, M.; et al. B-Raf activation cooperates with PTEN loss to drive c-Myc expression in advanced prostate cancer. *Cancer Res.* 2012, 72, 4765–4776. [CrossRef]

269. Jefferies, M.T.; Cox, A.C.; Shorning, B.Y.; Meniel, V.; Griffiths, D.; Kynaston, H.G.; Smalley, M.; Clarke, A.R. PTEN loss and activation of K-RAS and β-catenin cooperate to accelerate prostate tumourigenesis. *J. Pathol.* 2017, 243, 442–456. [CrossRef]

270. Toren, P.; Kim, S.; Johnson, F.; Zoubeidi, A. Combined AKT and MEK Pathway Blockade in Pre-Clinical Models of Enzalutamide-Resistant Prostate Cancer. *PLoS ONE* 2016, 11, e0152861. [CrossRef] [PubMed]

271. Turke, A.B.; Song, Y.; Costa, C.; Cook, R.; Arteaga, C.L.; Asara, J.M.; Engelman, J.A. MEK inhibition leads to PI3K/AKT activation by relieving a negative feedback on ERBB receptors. *Cancer Res.* 2012, 72, 3228–3237. [CrossRef] [PubMed]

272. Gioeli, D.; Wunderlich, W.; Sebolt-Leopold, J.; Bekiranov, S.; Wulfkuhle, J.D.; Petricoin, E.F.; Conaway, M.; Weber, M.J. Compensatory pathways induced by MEK inhibition are effective drug targets for combination therapy against castration-resistant prostate cancer. *Mol. Cancer Ther.* 2011, 10, 1581–1590. [CrossRef] [PubMed]

273. Crabb, S.J.; Birtle, A.J.; Martin, K.; Downs, N.; Ratcliffe, I.; Maisman, T.; Ellis, M.; Griffiths, G.; Thompson, S.; Ksiazek, L.; et al. ProCAID: A phase I clinical trial to combine the AKT inhibitor AZD5363 with docetaxel and prednisolone chemotherapy for metastatic castration resistant prostate cancer. *Investig. New Drugs* 2017, 35, 599–607. [CrossRef]

274. Gillesen, S.; Gilson, C.; James, N.D.; Adler, A.; Sydes, M.R.; Clarke, N. Repurposing Metformin as Therapy for Prostate Cancer within the STAMPEDE Trial Platform. *Eur. Urol.* 2016, 70, 906–908. [CrossRef] [PubMed]

275. Virollet, B.; Guigas, B.; Garcia, N.S.; Leclerc, J.; Foretz, M.; Andreelli, F. Cellular and molecular mechanisms of metformin: An overview. *Clin. Sci.* 2011, 122, 253–270. [CrossRef] [PubMed]

276. Soares, H.P.; Ni, Y.; Kisolatti, V.; Sennett-Smith, J.; Rozengurt, E. Different Patterns of Akt and ERK Feedback Activation in Response to Rapamycin, Active-Site mTOR Inhibitors and Metformin in Pancreatic Cancer Cells. *PLoS ONE* 2013, 8, e57289. [CrossRef] [PubMed]

277. Jokinen, E.; Koivunen, J. MEK and PI3K inhibition in solid tumors: Rationale and evidence to date. *Ther. Adv. Med. Oncol.* 2015, 7, 170–180. [CrossRef] [PubMed]

278. Bardia, A.; Gounder, M.; Rodon, J.; Janku, F.; Lolkema, M.P.; Stephenson, J.J.; Bedard, P.L.; Schuler, M.; Sessa, C.; Lorusso, P.; et al. Phase Ib Study of Combination Therapy with MEK Inhibitor Binimetinib and Phosphatidylinositol 3-Kinase Inhibitor Buparlisib in Patients with Advanced Solid Tumors with RAS/RAF Alterations. *Oncologist* 2019, 25, e160–e169. [CrossRef]

279. Tindall, N.J.; Lonergan, P.E. Androgen receptor signaling in prostate cancer development and progression. *J. Carcinog.* 2011, 10, 20. [CrossRef]

280. Zhou, Y.; Bolton, E.C.; Jones, J.O. Androgens and androgen receptor signaling in prostate tumorigenesis. *J. Mol. Endocrinol.* 2014, 54, R15–R29. [CrossRef]

281. Tan, E.; Li, J.; Xu, H.E.; Melcher, K.; Yong, E.-L. Androgen receptor: Structure, role in prostate cancer and drug discovery. *Acta Pharmacol. Sin.* 2014, 36, 3–23. [CrossRef] [PubMed]

282. Miller, W.L.; Auchus, R.J. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr. Rev.* 2010, 32, 81–151. [CrossRef] [PubMed]

283. 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]
284. Cai, C.; Balk, S.P. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. *Endocr. Relat. Cancer* 2011, 18, R175–R182. [CrossRef]

285. Dai, C.; Chung, Y.-M.; Kovac, E.; Zhu, Z.; Li, J.; Magi-Galluzzi, C.; Stephenson, A.J.; Klein, E.A.; Sharifi, N. Direct Metabolic Interrogation of Dihydrotestosterone Biosynthesis from Adrenal Precursors in Primary Prostatectomy Tissues. *Clin. Cancer Res.* 2017, 23, 6351–6362. [CrossRef]

286. Dehm, S.M.; Tindall, N.J. Androgen Receptor Structural and Functional Elements: Role and Regulation in Prostate Cancer. *Mol. Endocrinol.* 2007, 21, 2855–2863. [CrossRef]

287. Lamont, K.R.; Tindall, N.J. Minireview: Alternative activation pathways for the androgen receptor in prostate cancer. *Mol. Endocrinol.* 2011, 25, 897–907. [CrossRef]

288. Zamagni, A.; Cortesi, M.; Zanoni, M.; Tesei, A. Non-nuclear AR Signaling in Prostate Cancer. *Front. Chem.* 2019, 7, 651. [CrossRef]

289. 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]

290. Saranyutanon, S.; Srivastava, S.K.; Pai, S.; Singh, S.; Singh, A.P. Therapies Targeted to Androgen Receptor Signaling Axis in Prostate Cancer: Progress, Challenges, and Hope. *Cancers* 2019, 12, 51. [CrossRef]

291. Murillo, H.; Huang, H.; Schmidt, L.J.; Smith, D.I.; Tindall, N.J. Role of PI3K Signaling in Survival and Progression of LNCaP Prostate Cancer Cells to the Androgen Refractory State. *Endocrinology* 2001, 142, 4795–4805. [CrossRef]

292. Zoubeidi, A.; Gleave, M. Co-targeting driver pathways in prostate cancer: Two birds with one stone. *EMBO Mol. Med.* 2018, 10, e8928. [CrossRef] [PubMed]

293. Audet-Walsh, E.; Dufour, C.R.; Yee, T.; Zouanat, F.Z.; Yan, M.; Kalloghlian, G.; Vernier, M.; Caron, M.; Bourque, G.; Scarlata, E.; et al. Nuclear mTOR acts as a transcriptional integrator of the androgen signaling pathway in prostate cancer. *Genes Dev.* 2017, 31, 1228–1242. [CrossRef] [PubMed]

294. Qi, W.; Morales, C.; Cooke, L.S.; Johnson, B.; Somer, B.; Mahadevan, D. Reciprocal feedback inhibition of the androgen receptor and PI3K as a novel therapy for castrate-sensitive and -resistant prostate cancer. *Oncotarget* 2015, 6, 41976–41987. [CrossRef] [PubMed]

295. Thomas, C.; Lamoureux, F.; Craffer, C.; Davies, B.R.; Beraldi, E.; Fazli, L.; Kim, S.; Thaper, D.; Gleave, M.E.; Zoubeidi, A. Synergistic Targeting of PI3K/AKT Pathway and Androgen Receptor Axis Significantly Delays Castration-Resistant Prostate Cancer Progression In Vivo. *Mol. Cancer Ther.* 2013, 12, 2342–2355. [CrossRef] [PubMed]

296. Yao, E.; Zhou, W.; Lee-Hoeflich, S.T.; Truong, T.; Haverty, P.M.; Eastham-Anderson, J.; Lewin-Koh, N.; Günter, B.; Belvin, M.; Murray, L.J.; et al. Suppression of HER2/HER3-Mediated Growth of Breast Cancer Cells with Combinations of GDC-0941 PI3K Inhibitor, Trastuzumab, and Pertuzumab. *Clin. Cancer Res.* 2009, 15, 4147–4156. [CrossRef]

297. Mahajan, N.P.; Liu, Y.; Majumder, S.; Warren, M.R.; Parker, C.E.; Mohler, J.L.; Earp, H.S.; Whang, Y.E. Activated Cdc42-associated kinase Ack1 promotes prostate cancer progression via androgen receptor tyrosine phosphorylation. *Proc. Natl. Acad. Sci. USA* 2007, 104, 8438–8443. [CrossRef]

298. Mellingho, I.K.; Vivanco, I.; Kwon, A.; Tran, C.; Wongvipat, J.; Sawyers, C.L. HER2/neu kinase-dependent modulation of androgen receptor function through effects on DNA binding and stability. *Cancer Cell* 2004, 6, 517–527. [CrossRef]

299. Yeh, S.; Lin, H.-K.; Kang, H.-Y.; Thin, T.H.; Chang, C. From HER2/Neu signal cascade to androgen receptor and its coactivators: A novel pathway by induction of androgen target genes through MAP kinase in prostate cancer cells. *Proc. Natl. Acad. Sci. USA* 1999, 96, 5458–5463. [CrossRef]

300. Liu, P.; Li, S.; Gan, L.; Kao, T.P.; Huang, H. A Transcription-Independent Function of FOXO1 in Inhibition of Androgen-Independent Activation of the Androgen Receptor in Prostate Cancer Cells. *Cancer Res.* 2008, 68, 10290–10299. [CrossRef]

301. Bowen, C.; Ostrowski, M.C.; Leone, G.; Gelmann, E.P. Loss of PTEN Accelerates NKKX3.1 Degradation to Promote Prostate Cancer Progression. *Cancer Res.* 2019, 79, 4124–4134. [CrossRef] [PubMed]

302. Tan, P.Y.; Chang, C.W.; Chng, K.R.; Wansa, K.D.S.A.; Sung, W.-K.; Cheung, E. Integration of Regulatory Networks by NKKX3-1 Promotes Androgen-Dependent Prostate Cancer Survival. *Mol. Cell. Biol.* 2011, 32, 399–414. [CrossRef] [PubMed]
316. Wei, X.X.; Jiao, J.; Xin, L.; Chang, C.-J.; Wang, S.; Gao, J.; Gleave, M.E.; Witte, O.N.; Liu, X.; Wu, H. NXX3.1 stabilizes p53, inhibits AKT activation, and blocks prostate cancer initiation caused by PTEN loss. Cancer Cell 2006, 9, 367–378. [CrossRef] [PubMed]

303. Lei, Q.-Y.; Jiao, J.; Xin, L.; Chang, C.-J.; Wang, S.; Gao, J.; Gleave, M.E.; Witte, O.N.; Liu, X.; Wu, H. NXX3.1 stabilizes p53, inhibits AKT activation, and blocks prostate cancer initiation caused by PTEN loss. Cancer Cell 2006, 9, 367–378. [CrossRef] [PubMed]

304. Wang, Q.; Bailey, C.; Ng, C.; Tiffen, J.; Thoeng, A.; Minhas, V.; Lehman, M.L.; Hendy, S.C.; Buchanan, G.; Nelson, C.C.; et al. Androgen Receptor and Nutrient Signaling Pathways Coordinate the Demand for Increased Amino Acid Transport during Prostate Cancer Progression. Cancer Res. 2011, 71, 7525–7536. [CrossRef] [PubMed]

305. Wen, Y.; Hu, M.C.; Makino, K.; Spohn, B.; Bartholomeusz, G.; Yan, D.H.; Hung, M.C. HER-2/neu promotes androgen-independent survival and growth of prostate cancer cells through the Akt pathway. Cancer Res. 2000, 60, 6841–6845. [PubMed]

306. Lin, H.-K.; Yeh, S.; Kang, H.-Y.; Chang, C. Akt suppresses androgen-induced apoptosis by phosphorylating and inhibiting androgen receptor. Proc. Natl. Acad. Sci. USA 2001, 98, 7200–7205. [CrossRef] [PubMed]

307. Blattner, M.; Liu, D.; Robinson, B.D.; Huang, D.; Poliakov, A.; Gao, D.; Nataraj, S.; Deonarine, L.D.; Augello, M.A.; Sailer, V.; et al. SPOP Mutation Drives Prostate Tumorigenesis In Vivo through Coordinate Regulation of PI3K/mTOR and AR Signaling. Cancer Cell 2017, 31, 436–451. [CrossRef]

308. Mani, R.S. The emerging role of speckle-type POZ protein (SPOP) in cancer development. Drug Discov. Today 2014, 19, 1498–1502. [CrossRef]

309. Agoulnik, I.U.; Weigel, N.L. Coactivator selective regulation of androgen receptor activity. Steroids 2009, 74, 669–674. [CrossRef]

310. Ferry, C.; Gaouar, S.; Fischer, B.; Boeglin, M.; Paul, N.; Samarut, E.; Piskunov, A.; Pankotai-Bodó, G.; Brino, L.; Rochette-Egly, C. Cullin 3 mediates SRC-3 ubiquitination and degradation to control the retinoid acid response. Proc. Natl. Acad. Sci. USA 2011, 108, 20603–20608. [CrossRef]

311. An, J.; Wang, C.; Deng, Y.; Yu, L.; Huang, H. Destruction of full-length androgen receptor by wild-type SPOP, but not prostate-cancer-associated mutants. Cell Rep. 2014, 6, 657–669. [CrossRef] [PubMed]

312. Baron, S.; Manin, M.; Beaudoin, C.; Leotoing, L.; Communal, Y.; Veyssiere, G.; Morel, L. Androgen Receptor Mediates Non-genomic Activation of Phosphatidylinositol 3-OH Kinase in Androgen-sensitive Epithelial Cells. J. Biol. Chem. 2003, 278, 14579–14586. [CrossRef] [PubMed]

313. Kolinsky, M.; Recsing, P.; Bianchini, D.; Zafeiriou, Z.; Mehra, N.; Mateo, J.; Michalarea, V.; Riisnaes, R.; Crespo, M.; Figueiredo, I.; et al. A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer. Ann. Oncol. 2020, 31, 619–625. [CrossRef] [PubMed]

314. Lawrence, 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] [PubMed]

315. Massard, C.; Chi, K.N.; Castellano, D.; De Bono, J.; Gravis, G.; Dirix, L.; Machiels, J.-P.; Mita, A.; Mellado, B.; Turri, S.; et al. Phase I trial of the PI3 kinase inhibitor BKM120 (BEZ235) in patients with prostate cancer. Eur. J. Cancer 2017, 81, 228–236. [CrossRef] [PubMed]

316. Wei, X.X.; Hsieh, A.C.; Kim, W.; Friedlander, T.; Lin, A.M.; Louttit, M.; Ryan, C.J. A Phase I Study of Abiraterone Acetate Combined with BEZ235, a Dual PI3K/mTOR Inhibitor, in Metastatic Castration Resistant Prostate Cancer. Oncologist 2017, 22, 503-e43. [CrossRef]

317. O’Sullivan, J.; Bose, S.; Cranford, M.; Feng, L.; Ali, S.; et al. Phase IIb dose-finding study of abiraterone acetate plus BKM120 (BEZ235) in patients with prostate cancer. Oncologist 2017, 22, 503-e43. [CrossRef]

318. Clevers, H.; Loh, K.M.; Nusse, R. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. Science 2014, 346, 1248012. [CrossRef]

319. Nusse, R.; Clevers, H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. Cell 2017, 169, 985–999. [CrossRef]

320. Murillo-Garzón, V.; Kryp, R. Wnt signaling in prostate cancer. Nat. Rev. Urol. 2017, 14, 683–696. [CrossRef]

321. Stamos, J.L.; Weis, W. The β-Catenin Destruction Complex. Cold Spring Harb. Perspect. Biol. 2012, 5, a007898. [CrossRef] [PubMed]
322. Schneider, J.A.; Logan, S.K. Revisiting the role of Wnt/β-catenin signaling in prostate cancer. *Mol. Cell. Endocrinol.* **2017**, *462*, 3–8. [CrossRef] [PubMed]

323. Ahmad, I.; Sansom, O.J. Role of Wnt signalling in advanced prostate cancer. *J. Pathol.* **2018**, *245*, 3–5. [CrossRef] [PubMed]

324. Zhang, Z.; Cheng, L.; Li, J.; Farah, E.; Lanman, N.A.; Pascuzzi, P.; Gupta, S.; Liu, X. Inhibition of the Wnt/β-catenin pathway overcomes resistance to enzalutamide in castration-resistant prostate cancer. *Cancer Res.* **2018**, *78*, 3147–3162. [CrossRef] [PubMed]

325. Velho, P.I.; Fu, W.; Wang, H.; Mirkheshti, N.; Qazi, F.; Lima, F.A.; Shaukat, F.; Carducci, M.A.; Denmeade, S.R.; Paller, C.J.; et al. Wnt-pathway activating mutations are associated with resistance to First-line abiraterone and enzalutamide in castration-resistant prostate cancer. *Eur. Urol.* **2019**, *77*, 14–21. [CrossRef] [PubMed]

326. Rajan, P.; Sudbery, I.; Villasevil, M.E.M.; Mui, E.; Fleming, J.; Davis, M.; Ahmad, I.; Edwards, J.; Sansom, O.J.; Bilir, B.; Osunkoya, A.O.; Wiles, W.G.; Sannigrahi, S.; Lefebvre, V.; Metzger, D.; Spyropoulos, D.D.; Martin, W.D.; Moreno, C.S. SOX4 Differentially Regulates β-Catenin/T-Cell Factor Activity and Proliferation of Colon Carcinoma Cells. *Mol. Cell. Biol.* **2015**, *27*, 7802–7815. [CrossRef]

327. Song, L.-N.; Gelmann, E.P. Interaction of β-Catenin and TIF2/GRIP1 in Transcriptional Activation by the Androgen Receptor. *J. Biol. Chem.* **2005**, *280*, 37853–37867. [CrossRef]

328. Yang, X.; Chen, M.-W.; Terry, S.; Vacherot, F.; Bemis, D.L.; Capodice, J.; Kitajewski, J.; De La Taille, A.; Benson, M.C.; Guo, Y.; et al. Complex regulation of human androgen receptor expression by Wnt signaling in prostate cancer cells. *Oncogene* **2006**, *25*, 3436–3444. [CrossRef]

329. Wang, G.; Wang, J.; Sadar, M.D. Crosstalk between the androgen receptor and beta-catenin in castrate-resistant prostate cancer. *Cancer Res.* **2008**, *68*, 9918–9927. [CrossRef]

330. Patel, R.; Brzezinska, E.A.; Repisck, P.; Ahmad, I.; Mui, E.; Gao, M.; Blomme, A.; Harle, V.; Tan, E.H.; Malviya, G.; et al. Activation of β-Catenin Cooperates with Loss of Pten to Drive AR-Independent Castration-Resistant Prostate Cancer. *Cancer Res.* **2019**, *80*, 576–590. [CrossRef] [PubMed]

331. Pearson, H.; Phesse, T.J.; Clarke, A. K-ras and Wnt Signaling Synergize to Accelerate Prostate Tumorigenesis in the Mouse. *Cancer Res.* **2009**, *69*, 94–101. [CrossRef] [PubMed]

332. Bruxvoort, K.J.; Charbonneau, H.M.; Giambernardi, T.A.; Goosby, J.C.; Qian, C.-N.; Zylstra, C.R.; Robinson, D.R.; Roy-Burman, P.; Shaw, A.; Buckner-Berghuis, B.D.; et al. Inactivation of Apc in the Mouse Prostate Causes Prostate Carcinoma. *Cancer Res.* **2007**, *67*, 2490–2496. [CrossRef] [PubMed]

333. Tenbaum, S.P.; Ordóñez-Morán, P.; Puig, I.; Chicote, I.; Arqués, O.; Landolfi, S.; Fernández, Y.; Camacho, J.R.H.; Gispert, J.D.; Mendizabal, I.; et al. β-catenin confers resistance to PI3K and AKT inhibitors and subverts FOXO3a to promote metastasis in colon cancer. *Nat. Med.* **2012**, *18*, 892–901. [CrossRef] [PubMed]

334. Persad, A.; Venkateswaran, G.; Hao, L.; Garcia, M.E.; Yoon, J.; Sidhu, J.; Persad, S. Active β-catenin is regulated by the PTEN/PI3 kinase pathway: A role for protein phosphatase PP2A. *Genes Cancer* **2017**, *7*, 368–382. [CrossRef]

335. Liu, H.; Yin, J.; Wang, H.; Jiang, G.; Deng, M.; Zhang, G.; Bu, X.; Cai, S.; Du, J.; He, Z. FOXO3a modulates WNT/β-catenin signaling and suppresses epithelial-to-mesenchymal transition in prostate cancer cells. *Cell. Signal.* **2015**, *27*, 510–518. [CrossRef]

336. Sinner, D.; Kordich, J.J.; Spence, J.R.; Opopka, R.; Rankin, S.; Lin, S.-C.J.; Jonatan, D.; Zorn, A.M.; Wells, J.M. Sox17 and Sox4 Differentially Regulate β-Catenin/T-Cell Factor Activity and Proliferation of Colon Carcinoma Cells. *Mol. Cell. Biol.* **2015**, *27*, 7802–7815. [CrossRef]

337. Conde-Perez, A.; Gisselbrecht, C.; Pedersen, M.; Petit, V.; Aktary, Z.; Viros, A.; Gesbert, F.; Delmas, V.; Rambow, F.; et al. A caveolin-dependent and PI3K/AKT-independent role of PTEN in β-catenin transcriptional activity. *Nat. Commun.* **2015**, *6*, 8093. [CrossRef]

338. Wu, D.; Pan, W. GSK3: A multifaceted kinase in Wnt signaling. *Trends Biochem. Sci.* **2010**, *35*, 161–168. [CrossRef]

339. Buller, C.L.; Loberg, R.D.; Fan, M.-H.; Zhu, Q.; Park, J.L.; Vesely, E.; Inoki, K.; Guan, K.-L.; Brosius, F.C. A GSK-3/TSC2/mTOR pathway regulates glucose uptake and GLUT1 glucose transporter expression. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, C836–C843. [CrossRef]
342. Evangelisti, C.; Chiarini, F.; Paganelli, F.; Marmirol, S.; Martelli, A.M. Crosstalks of GSK3 signaling with the mTOR network and effects on targeted therapy of cancer. *Biochim. Biophys. Acta Mol. Cell Res.* 2020, 1867, 118635. [CrossRef] [PubMed]

343. Ding, V.W.; Chen, R.-H.; McCormick, F. Differential Regulation of Glycogen Synthase Kinase 3β by Insulin and Wnt Signaling. *J. Biol. Chem.* 2000, 275, 32475–32481. [CrossRef]

344. Griend, D.V.; Litvinov, I.V.; Isaacs, J.T. Conversion of Androgen Receptor Signaling From a Growth Suppressor to an Oncogene in Prostate Cancer Cells Involves a Gain of Function in c-Myc Regulation. *Int. J. Biol. Sci.* 2014, 10, 627–642. [CrossRef] [PubMed]
362. Antony, L.; Van Der Schoor, F.; Dalrymple, S.L.; Isaacs, J.T. Androgen receptor (AR) suppresses normal human prostate epithelial cell proliferation via AR/β-catenin/TCF-4 complex inhibition of c-MYC transcription. *Prostate* **2014**, *74*, 1118–1131. [CrossRef] [PubMed]

363. Barfeld, S.J.; Urbanucci, A.; Itkonen, H.M.; Fazli, L.; Hicks, J.L.; Thiede, B.; Rennie, P.S.; Yegnasubramanian, S.; DeMarzo, A.M.; Mills, I.G. c-Myc Antagonises the Transcriptional Activity of the Androgen Receptor in Prostate Cancer Affecting Key Gene Networks. *EBioMed.* **2017**, *18*, 83–93. [CrossRef] [PubMed]

364. Rebello, R.J.; Pearson, R.B.; Hannan, R.D.; Furic, L. Therapeutic Approaches Targeting MYC-Driven Prostate Cancer. *Genes* **2017**, *8*, 71. [CrossRef]

365. 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]