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Review Article

From genomics to functions: preclinical mouse models for understanding oncogenic pathways in prostate cancer

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Abstract: Next-generation sequencing has revealed numerous genomic alterations that induce aberrant signaling activities in prostate cancer (PCa). Among them are pathways affecting multiple cancer types, including the PI3K/AKT/mTOR, p53, Rb, Ras/Raf/MAPK, Myc, FGF, and Wnt signaling pathways, as well as ones that are prominent in PCa, including alterations in genes of AR signaling, the ETS family, *NKX3.1*, and *SPOP*. Cross talk among the oncogenic pathways can confer PCa resistance to therapy, particularly in advanced tumors, which are castration-resistant or show neuroendocrine features. Various experimental models, such as cancer cell lines, animal models, and patient-derived xenografts and organoids have been utilized to dissect PCa progression mechanisms. Here, we review the current preclinical mouse models for studying the most commonly altered pathways in PCa, with an emphasis on their interplays. We highlight the power of genetically engineered mouse models (GEMMs) in translating genomic discoveries into understanding of the functions of these oncogenic events in vivo. Developing and analyzing PCa mouse models will undoubtedly continue to offer new insights into tumor biology and guide novel rationalized therapy.

Keywords: Prostate, cancer progression, mouse models, castration-resistance, neuroendocrine, PI3K, AR, p53, Wnt, ETS

Introduction

Prostate cancer (PCa) is one of the most common malignancies in men of developed countries and is continuously increasing in developing countries [1]. Prostatic intraepithelial neoplasia (PIN), the precursor lesion to adenocarcinoma, can be present in men of young age. Most patients with early stage PCa undergo active surveillance, or are treated with radiation or radical prostatectomy. Androgen-deprivation therapy was first adopted by Huggins and Hodges in 1941 [2], and remains the first line treatment for advanced PCa. However, the inevitable recurrence of castration-resistant prostate cancer (CRPC) after androgen-deprivation therapy remains a major challenge, as treatment options are limited (**Figure 1**). Tumors that become androgen receptor (AR) independent may develop into neuroendocrine prostate cancer (NEPC), which is one of the most lethal subtypes of PCa [3]. Understanding the molecular mechanism of PCa progression is crucial for the development of effective therapies.

The prostate gland forms through budding from the urogenital sinus during development [4]. The mature prostate contains ductal structures consisting of a stromal compartment and an epithelium, from which adenocarcinomas arise. The normal prostate epithelium is primarily comprised of stratified basal cells and luminal cells identifiable by specific markers, as well as interspersed rare neuroendocrine cells [5]. Multiple cancer genomics studies have revealed the recurrent mutational events involved in PCa progression, such as *MYC* and *AR* amplification/overexpression, ETS family gene fusions, alterations in the TP53, PTEN, MAPK, and WNT pathways, and various mutations in *FOXA1*, *SPOP*, and genes of DNA repair and chromatin remodeling (**Figure 1**). Among them, TP53, WNT and AR pathway alterations are par-

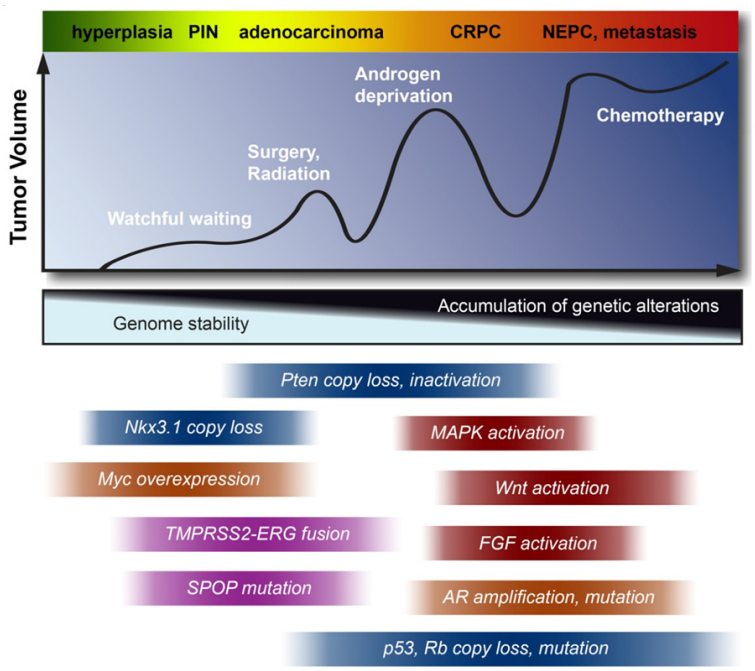

Figure 1. Overview of PCa stages, treatment options, and molecular alterations. Cancer progression in the prostate undergoes different stages from hyperplasia to metastatic tumor. Timing and the temporary effect on the tumor volume are shown for different treatment options at various stages. Genomics studies have revealed major molecular alterations in PCa, shown in their likely order during cancer progression. Color code indicates whether the alteration is loss-of-function or gain-of-function.

ticularly enriched in metastatic CRPC compared to primary PCa, and are believed to be late events [6-12].

In order to understand how various mutations and dysregulated signaling pathways affect PCa progression, different experimental models have been utilized. PCa cell lines are traditionally the most widely used models in PCa research and have been discussed in detail elsewhere [13-16]. Recent development of the organoid technology has enabled better in vitro modeling of prostate tumors from patient biopsies which recapitulate the molecular diversity of prostate cancer subtypes [17, 18]. In addition, xenograft models, in particular patient-derived xenografts (PDX) provide valuable resources to study PCa treatment responses and resistance [19, 20]. Finally, over the past two decades, genetically engineered mouse models (GEMMs) have been instrumental in revealing the functions of genetic alterations in promoting PCa progression in vivo. The NIH established the Mouse Models of Human Cancer Consortium (MMCC) in 1999. Since then, GEMMs of PCa have evolved from simple knockout and transgenic mice to complex conditional manipulation on multiple genes of interest in prostate-specific or cell-type-specific fashions. Similarities between mouse and human PCa progression are abundant, although differences such as the propensity of bone metastasis also exist. Below, we summarize GEMMs for the most frequently altered pathways found in human PCa (listed in **Table 1**) following the likely order of events during cancer progression, and discuss how they have contributed to our understanding of pathway interactions and therapeutic resistance mechanisms.

PI3K signaling pathway

PCa mouse models investigating the role of the PI3K/Akt/mTOR axis

The PI3K/Akt/mTOR axis is an important intracellular signaling pathway that drives cellular growth and survival, and its hyper-activation is common across many types of cancers. Nearly 50% of primary and metastatic PCas have aberrant PI3K signaling activities, commonly through copy-number loss of the *PTEN* tumor-suppressor gene [7, 10, 11]. Although PI3K activation is not the earliest event in PCa initiation, we discuss this pathway first since its activation is the single most extensively modeled event in PCa mouse studies, often serving as a baseline model for studying oncogenic cooperation.

Pten loss results in constitutive activation of downstream targets including the Akt kinase family [21]. Initially, knockout mice were generated to investigate the function of Pten in cancer. While *Pten-/-* mice are embryonic lethal, *Pten-/+* mice developed multiple types of tumors, and hyperplasia/dysplasia in the prostate [22, 23]. Later, the prostate-specific *Pb-Cre4* line [24] was used for *Pten* conditional knockout, and the *Pb-Cre; Pten*$^{fl/fl}$ model reli-

Table 1. List of GEMMs analyzing the functions and interactions of major altered signaling pathways in PCa

Pathways	References	Mouse model	Histology and interpretation
PI3K/Akt/mTOR	[22, 23]	*Pten-/+*	Hyperplasia/dysplasia, decreasing Pten level associated with worse phenotypes
	[30]	*$Pten^{hy/+}$* *$Pten^{hy/-}$*	
	[25]	*Pb-Cre; $Pten^{fl/fl}$*	Adenocarcinoma
	[28, 29]	*ARR2PB-$CreER^{T2}$; $Pten^{fl/fl}$* *PSA-$CreER^{T2}$; $Pten^{fl/fl}$*	PIN/adenocarcinoma
	[62, 63]	*CK5 (or CK14, CK8, Nkx3.1)-$CreER^{T2}$; $Pten^{fl/fl}$*	PIN/adenocarcinoma, with more aggressive phenotypes using luminal drivers
	[34]	*Pb-myrAkt1 (MPAKT)*	PIN
	[32]	*Pb-Cre; $p110\alpha^{fl/fl}$; $Pten^{fl/fl}$*	PIN
		Pb-Cre; $p110\beta^{fl/fl}$; $Pten^{fl/fl}$	Impairment of PIN formation
	[33]	*ARR2PB-MF-p110β*	PIN
	[37]	*Pten-/+; Rictor-/+* *Pb-Cre; $Pten^{fl/fl}$; $Rictor^{fl/fl}$*	Impairment of hyperplasia or PIN formation
	[38]	*Pb-Cre; $Pten^{fl/fl}$; $eIF4E^{S209A}$*	Impairment of hyperplasia or PIN formation
	[40]	*Pten-/+; Pml-/+*	Accelerated progression to PIN or adenocarcinoma
	[41]	*Pten-/+; Tsc2-/+*	Accelerated progression to PIN or adenocarcinoma
	[39]	*Pb-Cre; $Pten^{fl/fl}$; 4EBP1-/-; 4EBP2-/-*	Accelerated progression to PIN or adenocarcinoma
	[42]	*Pb-Cre; $Pten^{fl/fl}$; $Pik3ca^{H1047R/+}$*	Accelerated progression to PIN or adenocarcinoma
PI3K & p27	[45]	*Pten-/+; $p27^{Kip1}$-/+*	Accelerated PIN
	[46]	*MPAKT; $p27^{Kip1}$-/-*	Adenocarcinoma, overcome of senescence
PI3K & TGFβ	[52]	*Pb-Cre; $Pten^{fl/fl}$; $Smad4^{fl/fl}$*	Metastatic tumor
	[53]	*CK8-$CreER^{T2}$; $Pten^{fl/fl}$; $Tgfb2^{fl/fl}$*	Metastatic tumor
Other PI3K interactions	[47]	*Pb-Cre; $Pten^{fl/fl}$; $Her2^{KI}$*	Accelerated adenocarcinoma, overcome of senescence
	[48]	*Pb-Cre; $Pten^{fl/+}$; Z/Sox9*	Accelerated PIN
	[49-51]	*Pb-Cre; $Pten^{fl/fl}$; $Zbtb7a^{fl/fl}$*	Overcome of senescence, resistance to castration
	[56]	*Pb-Cre; $Pten^{fl/fl}$; $Whsc1^{fl/fl}$*	Impairment of PIN formation
		Pb-Cre; $Pten^{fl/fl}$; $Whsc1^{OE/+}$	Metastatic tumor
Myc	[70]	*Lo-Myc, Hi-Myc*	PIN/Adenocarcinoma
	[72]	*Pb-Cre; Z-Myc*	PIN
PI3K & Myc		*Pb-Cre; $Pten^{fl/fl}$; Z-Myc*	Accelerated PIN/Adenocarcinoma
	[75]	*Pb-Cre; $Pten^{fl/fl}$; Hi-Myc*	Accelerated PIN/Adenocarcinoma
PI3K & N-Myc	[79]	*Pb-Cre; $Pten^{fl/fl}$; $R26^{LSL\text{-}MYCN}$*	Neuroendocrine prostate cancer
Nkx3.1	[84-90]	*Nkx3.1-/+ or Nkx3.1-/-* *PSA-Cre; $Nkx3.1^{fl/fl}$*	PIN
PI3K & Nkx3.1	[89-92]	*Nkx3.1-/-; Pten+/-*	Adenocarcinoma in aged mice
ETS	[98, 99]	*ARR2PB-ETV1*	PIN
	[100, 101]	*ARR2Pb-ERG*	PIN of various degrees
	[102, 103]	*ARR2Pb-ERG*	Mostly normal morphology
	[104]	*Pb-Cre; $R26^{ERG/ERG}$*	Mostly normal morphology
	[105-107]	*Tg (TMPRSS2-ERG)*	Mostly normal morphology
PI3K & ETS	[103]	*ARR2Pb-ERG; Pten+/-*	Accelerated progression to PIN/Adenocarcinoma
	[104]	*Pb-Cre; $Pten^{fl/fl}$; $R26^{ERG/ERG}$*	Accelerated progression to PIN/Adenocarcinoma
	[105]	*KI (TMPRSS2-ERG); Pten-/+* *KI (TMPRSS2-ERG); Pb-Cre; $Pten^{fl/fl}$*	Accelerated progression to PIN/Adenocarcinoma
	[106]	*ARR2Pb-TMPRSS2-ERG; Pten+/-*	Accelerated progression to PIN/Adenocarcinoma
	[111]	*Pb-Cre; $Ets2^{fl/fl}$; $Pten^{fl/fl}$*	Accelerated progression to PIN/Adenocarcinoma
SPOP	[115]	*Pb-Cre; $Spop^{fl/fl}$*	PIN, upregulation of AR and Myc
	[116, 119]	*Pb-Cre; $R26^{SPOP\text{-}F133V}$*	Normal
PI3K & SPOP		*Pb-Cre; $Pten^{fl/fl}$; $R26^{SPOP\text{-}F133V}$*	Accelerated PIN
Wnt	[123-128]	*MMTV-Cre, Nkx3.1-Cre, Pb-Cre or $p63^{CreERT2/+}$; $Ctnnb1^{L(ex3)/L(ex3)}$*	Squamous metaplasia, PIN of varied degrees
	[130]	*Pb-Cre; $Apc^{fl/fl}$*	Adenocarcinoma
	[131]	*Ubi-Cat*	Adenocarcinoma

PI3K & Wnt	[129]	*Pb-Cre; Ctnnb$^{fl/fl}$; Pten$^{fl/fl}$*	No impairment of progression
		Pb-Cre; Ctnnb1$^{L(ex3)/L(ex3)}$; Pten$^{fl/fl}$	Accelerated adenocarcinoma
Wnt & p53/Rb	[126]	*Pb-Cre; Ctnnb1$^{L(ex3)/L(ex3)}$; LPB-Tag*	Adenocarcinoma with neuroendocrine feature
MAPK	[136]	*Pb-H-Ras^{G12V}*	Low grade PIN
Wnt & MAPK	[127]	*Pb-Cre; K-Ras$^{LSL-V12/+}$* *Pb-Cre; ctnnb1$^{+/lox(ex3)}$; K-Ras$^{LSL-V12/+}$*	Adenocarcinoma
MAPK & p16	[137]	*iBRAF**	Adenocarcinoma
PI3K & MAPK	[138, 141, 142]	*Pb-Cre; Pten$^{fl/fl}$; K-Ras$^{LSL-G12D/+}$*	Metastatic tumor
	[143]	*Nkx3.1$^{CreERT2/+}$; Pten$^{fl/fl}$; K-Ras$^{LSL-G12D/+}$*	Metastatic tumor
FGF	[152, 153]	*Pb-Fgf7, Pb-Fgf8, Pb-Fgfr2iib*	PIN, Fgfr1 and Fgfr2iib synergize to promote high grade PIN
	[154-157]	*Pb-Fgfr1*	PIN, Fgfr1 and Fgfr2iib synergize to promote high grade PIN
PI3K & FGF	[158]	*ARR2PB-Fgf8b; Pb-Cre; Pten$^{fl/+}$*	Metastatic tumor
Wnt & FGF	[159]	*Ubi-Cat; JOCK1*	Accelerated adenocarcinoma with reactive stroma
Tp53/Rb	[43, 76, 169]	*Pb-Cre; p53$^{fl/fl}$*	Normal
	[170]	*Pb-p53^{R273H}*	PIN
	[171]	*Nkx3.1-Cre; p53$^{LSL-R270H/R270H}$*	PIN
	[176]	*Pb-Cre; Rb$^{fl/fl}$*	Hyperplasia
	[177-179]	*TRAMP, LADY*	Metastatic tumor with neuroendocrine feature
	[169, 185]	*Pb-Cre; p53$^{fl/fl}$; Rb$^{fl/fl}$*	Neuroendocrine tumor
PI3K & p53/Rb	[43, 50]	*Pb-Cre; Pten$^{fl/fl}$; p53$^{fl/fl}$*	Accelerated adenocarcinoma, bypass of senescence and castration-induced apoptosis
	[186, 187]	*Pb-Cre; Pten$^{fl/fl}$; Rb1$^{fl/fl}$* *Pb-Cre; Pten$^{fl/fl}$; Rb1$^{fl/fl}$; p53$^{fl/fl}$*	Metastatic tumor with neuroendocrine feature
AR	[190]	*Pb-mAR*	Low grade PIN at old age
	[191]	*Osr1-Cre; R26-LSL-AR*	PIN/adenocarcinoma
	[192]	*Pb-AR-E231G*	PIN
	[194]	*Pb-AR^{v567es}*	Adenocarcinoma at old age
	[195]	*ARR2PB-AR-V7*	PIN
Wnt & AR	[128, 215]	*Pb-Cre* or *p63$^{CreERT2/+}$; Ctnnb1$^{L(ex3)/+}$; R26hAR$^{L/+}$*	Accelerated adenocarcinoma
PI3K & AR	[212, 213]	*Pb-Cre; Pten$^{fl/fl}$; AR$^{fl/Y}$*	AR dispensable for Pten tumor progression. PI3K & AR form reciprocal negative feedback loop.
	[204, 214]	*Osr1-Cre; Pten$^{fl/fl}$; AR$^{fl/Y}$* *CK5-CreER^{T2}; Pten$^{fl/fl}$; AR$^{fl/Y}$* *Nkx3.1^{CreERT2}; Pten$^{fl/fl}$; AR$^{fl/Y}$*	AR dispensable for Pten tumor progression

ably developed invasive adenocarcinoma [25]. Studying murine cell lines derived from this model suggested that Pten loss bestows tumors androgen-independent proliferation [26]. In addition, this model also revealed that epithelial *Pten* deletion may trigger the secretion of inflammatory cytokines to promote the expansion of a subset of Gr-1^{+}CD11b^{+} myeloid-derived suppressor cells (MDSCs), leading to immune suppression and tumor progression [27]. It is worth noting that in this model *Pten* deletion occurs during prostate postnatal development due to the early timing of *Pb-Cre* activation. Indeed, when the inducible *ARR2PB-CreER^{T2}* or *PSA-CreER^{T2}* lines were used, *Pten* loss at the adult stage yielded less aggressive prostate tumors [28, 29]. Besides timing, *Pten* expression level can heavily influence PCa progression. Using hypomorphic *Pten* mutant mice *Pten^{hy}*, it was shown that decreasing Pten levels were correlated with progressively worse phenotypes (*Pten$^{hy/+}$* > *Pten$^{+/-}$* > *Pten$^{hy/-}$* > *Pten$^{prostate\text{-}knockout}$*) [30]. One possible mechanism of regulating Pten protein level is through the ubiquitin ligase NEDD4-1, which is strongly expressed in neoplastic areas of *Pten$^{hy/-}$* prostates [31].

Other components of the PI3K/Akt/mTOR axis have been modeled (**Figure 2**). PI3K class IA catalytic subunit p110α (PIK3CA) or p110β (PIK3CB) is frequently overexpressed in PCa [11]. Interestingly, conditional knockout of p110β, but not p110α, impeded Akt phosphorylation and Pten-loss-induced tumorigenesis [32], while overexpressing activated p110β in transgenic mice induced PIN phenotypes [33]. A transgenic mouse model overexpressing activated Akt1 under the probasin promoter (MPAKT) was developed, and mice only

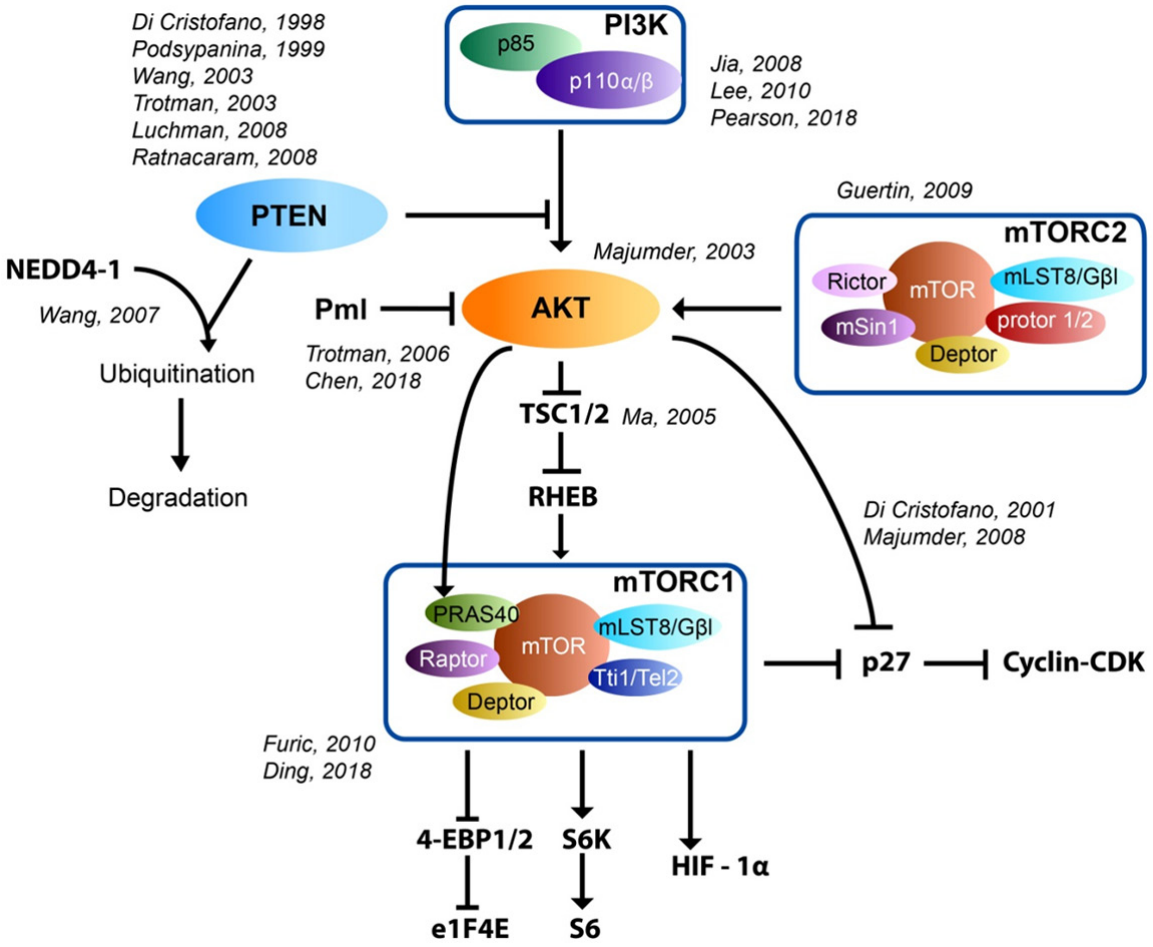

Figure 2. Mouse models used to study the PI3K/AKT/mTOR axis in PCa. Major components of the PI3K/AKT/mTOR pathway and their molecular signaling relationships are shown. Pioneer papers that described the GEM models of the individual components or their interactions are listed.

developed PIN in the ventral lobes [34]. Akt-induced cancer initiation is dependent on downstream mTOR activation since treatment with the mTOR inhibitor RAD001 reversed the PIN phenotype in MPAKT mice [35]. mTOR is a protein kinase that exists in two distinct complexes, the mTOR complex 1 (mTORC1) and mTORC2, and serves as a central regulator of cell metabolism and growth. The two complexes share certain protein subunits, with Rictor being one of the components in mTORC2 [36]. Double mutant mice *Pten-/+; Rictor-/+* and *Pb-Cre; Pten*$^{fl/fl}$*; Rictor*$^{fl/fl}$ showed dramatically reduced tumor phenotypes compared to their respective models of single *Pten* mutant, suggesting an essential role of mTORC2 in transducing the PI3K signal in *Pten*-loss tumors [37]. On the other hand, mTORC1 can phosphorylate 4E-BP1 and 4E-BP2, preventing them from binding and inhibiting eIF4E, a factor promoting protein synthesis. To study the role of eIF4E, a knock-in model *eIF4E*^{S209A} was built to mutate its only phosphorylation site, and this was sufficient to inhibit the Pten-loss-induced PCa progression [38]. Interestingly, in *Pb-Cre; Pten*$^{fl/fl}$*; 4EBP1-/-; 4EBP2-/-* mice, 4E-BP1/2 knockout significantly accelerated PCa progression from Pten loss, suggesting 4E-BP1/2 are tumor-suppressing even under constitutive mTORC1 activation, possibly due to their dephosphorylation under hypoxia conditions [39]. The accelerated PCa progression compared to Pten loss alone was also seen in *Pten-/+; Pml-/+* mice, which had reduced Akt antagonizer Pml [40], *Pten-/+; Tsc2-/+* mice, which had reduced mTOR antagonizer Tsc2 [41], and *Pten* conditional knockout mice that overexpressed a mutant p110α (Pik3ca^{H1047R}) [42]. Overall, these findings suggest that PCa progression is very sensitive to the activity lev-

els of Akt and mTOR, and alterations of other components in the PI3K pathway are not functionally redundant to Pten loss.

Models of other regulators that cooperate with the PI3K pathway

Although the PI3K/Akt/mTOR axis plays a pivotal role in driving prostate adenocarcinoma formation, Pten loss can induce p53-dependent cell senescence response to prevent further progression [43]. We will discuss this and other major pathway interactions in later individual sections. Here, we briefly list a few other regulators that help keep the *Pten*-null tumors in check.

In many tissues, $p27^{Kip1}$ functions as a negative regulator of cyclin-CDK activity to inhibit cell cycle progression. Disruption of $p27^{Kip1}$ led to prostatic hyperplasia in *p27^{Kip1}-/-* mice [44], and *Pten-/+; p27^{Kip1}-/+* mice displayed accelerated neoplastic transformation [45]. Notably, $p27^{Kip1}$ and senescence marker levels increased in MPAKT mice, and *MPAKT; p27^{Kip1}-/-* mice developed invasive PCa, suggesting that a $p27^{Kip1}$-driven checkpoint limits progression from PIN to PCa [46]. Another event that can overcome Pten-loss-induced cell senescence is the activation of the receptor tyrosine kinase Her2, as conditional expression of activated Her2 in *Pb-Cre; Pten$^{fl/fl}$; Her2^{KI}* mice activated the MAPK pathway and led to faster progression [47].

Transcription factor Sox9 is expressed in certain human PCa specimens and is correlated with decreased survival. Prostate-specific Sox9 overexpression was shown to cooperate with one copy loss of *Pten* in transformation in *Pb-Cre; Pten$^{fl/+}$; Z/Sox9* mice [48]. One factor that can inhibit Sox9-dependent oncogenic pathways is Zbtb7a, as its homozygous deletion led to bypass of *Pten*-loss-induced cellular senescence [49] and resistance to castration in the Pten-null tumors [50]. Recently, loss of Zbtb7a was also shown to trigger the infiltration of $Gr1^{+}CD11b^{+}$ immune cells through CXCL5 up-regulation in *Pb-Cre; Pten$^{fl/fl}$; Zbtb7a$^{fl/fl}$* mice to promote tumor progression [51].

Regarding PCa metastasis, TGFβ/Smad4 signaling has been shown to serve as a barrier for *Pten*-null tumors. *Pb-Cre; Pten$^{fl/fl}$; Smad4$^{fl/fl}$* mice developed metastasis to the lymph nodes and lung with high penetrance [52], and inactivating TGFβ receptor in luminal cells in *CK8-CreER^{T2}; Pten$^{fl/fl}$; Tgfb2$^{fl/fl}$* mice enhanced metastasis and luminal cell dedifferentiation [53]. Another gene that was shown to drive *Pten*-null tumors towards metastasis is *Whsc1*, a histone methyltransferase overexpressed in a number of metastatic tumors [54, 55]. Prostate-specific ablation of *Whsc1* prevented tumor progression in *Pb-Cre; Pten$^{fl/fl}$; Whsc1$^{fl/fl}$* mice, while its overexpression promoted tumor metastasis in *Pb-Cre; Pten$^{fl/fl}$; Whsc1$^{OE/+}$* mice [56]. Mechanistically, Pten-loss-induced Akt activation stabilizes Whsc1 from degradation via phosphorylation, and allows Whsc1 to transcriptionally upregulate Rictor, forming a positive-feedback loop through mTORC2 to further enhance Akt activity [56].

PI3K-based mouse models for studying PCa cell of origin

It has been appreciated in multiple cancers that the cell of origin, defined as a normal cell that can give rise to a tumor upon transformation, plays a major role in determining tumor subtype and outcome [57]. Although PCa shows a predominantly luminal phenotype, tumors originating from basal and luminal cells may be distinguishable by their agressiveness and such information may be useful for prognosis [58]. Transplantation-based studies, in which basal and luminal cells were renal-grafted in immunodeficient mice, mostly reported basal cells to be more aggressive in cancer initiation [59-61]. However, the renal-graft assay intrinsically disfavors luminal cell growth, and lacks the intact tumor microenvironment in GEMMs. To test the cell of origin in situ, cell-type-specific inducible Cre lines have been used to knockout *Pten* in either basal or luminal cells of the mouse prostate. In one study, basal-lineage-traced *K14-CreER^{T2}; Pten$^{fl/fl}$; mTmG* mice and luminal-lineage-traced *K8-CreER^{T2}; Pten$^{fl/fl}$; mTmG* mice were analyzed. Luminal cells were found to be more responsive to Pten-null induced mitogenic signaling, while basal cells underwent luminal differentiation before transformation [62]. Similar results were also observed by comparing *CK5-CreER^{T2}; Pten$^{fl/fl}$; R26R-YFP/+* and *Nkx3.1$^{CreERT2/+}$; Pten$^{fl/fl}$; R26R-YFP/+* mice, where luminal-derived tumors progressed faster and showed a gene signature predictive of poor outcomes in patients [63].

Notably, the relative susceptibility of luminal cells to oncogenic transformation is not restricted to the Pten-loss models, as a comparative lineage-tracing study showed that luminal cells are favored to be the cell of origin for PCa in multiple genetic and chemical-induced models [64].

Early oncogenic events in PCa initiation

Recent research suggests that prostate carcinogenesis favors the dysregulation of cancer genes in defined orders [65]. In this section, we discuss how modeling some of the early oncogenic events has led to a deeper understanding of the mechanisms underlying the transitions from normal prostate to PIN and subsequently to adenocarcinoma.

Myc up-regulation

The Myc transcription factor responds to diverse mitogenic and developmental signals to coordinate expression of diverse genes important for the orderly proliferation of somatic cells [66]. Myc expression is highly regulated, and changes of its expression level can influence somatic cell proliferation and oncogenesis [67, 68]. Up-regulation of c-Myc appears to be an early event in human PIN [69], and the gene is within the most commonly amplified loci on 8q24.21 in advanced PCa [10]. As a functional confirmation, transgenic mice of Myc overexpression under the probasin promoters (*Lo-Myc* and *Hi-Myc*) displayed PIN and progressed to invasive adenocarcinoma [70]. Two other models, the transgenic *C(3)1-c-Myc* [71] and the inducible *Pb-Cre; Z-Myc* mice [72] showed much milder PIN phenotypes, possibly due to the different expression levels or mouse backgrounds. Nevertheless, up-regulation of Myc needs to cooperate with other oncogenic pathways for PCa to progress. Myc overexpression synergized with PIM1 kinase expression [73] and myrAkt expression [59, 74] in lentiviral-transfected renal grafts. In GEMMs, *Pb-Cre; Pten$^{fl/fl}$; Hi-Myc* bigenic mice showed faster tumor progression than either of the single lesion models [75]. Z-Myc also cooperates with Pten loss [72]. Interestingly, in *Pb-Cre; Z-Myc; Pten$^{fl/+}$; p53$^{fl/+}$* triple mutant mice, loss of the wild-type *Pten* allele occurred prior to *p53* [76]. The order of these oncogenic events is consistent with findings in humans, and suggests a greater selective advantage to the tumor cell by Pten loss than p53 loss.

Unlike c-Myc, N-Myc was proposed to be involved in the development of NEPC [77]. Indeed, introduction of N-Myc and activated AKT1 into human prostate cells was sufficient to transform them into NEPC in renal grafts [78]. In *Pb-Cre; Pten$^{fl/fl}$; R26$^{LSL\text{-}MYCN}$* mice, overexpression of N-Myc when Pten is lost led to the development of poorly differentiated, invasive NEPC through the Ezh2-mediated transcriptional program [79]. This study, and others which are discussed later in the section of the p53 and Rb pathways, provide excellent examples of using GEMM to understand the mechanism behind transition from CRPC to NEPC as a treatment resistance.

Nkx3.1 down-regulation

The homeobox gene *Nkx3.1* is a key regulator in prostate development and tumorigenesis and is located within a region on chromosome 8p21.2 that frequently undergoes loss-of-heterozygosity in PIN lesions [80-82]. Although *Nkx3.1* is rarely mutated in primary PCa [9], its down-regulation is correlated with PCa initiation and progression [83]. *NKX3.1-/+*, *Nkx-3.1-/-*, and *PSA-Cre; Nkx-3.1$^{fl/fl}$* mice all developed PIN lesions [84-90], supporting an initiating role of Nkx3.1 loss-of-function in prostate tumorigenesis. *Nkx3.1-/-; Pten+/-* mice were prone to develop adenocarcinoma in aged mice [89-92], emphasizing the importance of the PI3K pathway in driving the progression of Nkx3.1-deficient tumors. In fact, loss of Pten alone leads to Nkx3.1 down-regulation at the transcriptional level [25, 93, 94]. Decreased Nkx3.1 expression was also observed in prostate tumors but not PINs of *Hi-Myc* mice, raising the possibility that Myc gain and Nkx3.1 loss may be cooperating events in the PIN to adenocarcinoma transition [70]. Mechanistically, in cancer cell line and xenograft models, Nkx-3.1 has been shown to negatively modulates AR transcription and stabilize p53 to impede cancer progression [94].

Genomic rearrangement of ETS family genes

Fusions of the *TMPRSS2* gene to the ETS family transcription factor genes *ERG*, *ETV1*, *ETV4* and *ETV5* are frequent chromosome rearran-

gement events in human PCa, accounting for 50-60% of all cases [95]. The most common gene fusion is *TMPRSS2-ERG*, which allows androgens to drive expression of the N-terminally truncated ERG protein in the prostate [95-97]. The presence of this fusion in benign prostatic hyperplasia and PIN cases indicates that it can be a relatively early event in prostate tumorigenesis.

Transgenic mouse models were established to functionally test the role of ETS genes. The *ARR2Pb* promoter was used to drive full-length and truncated ETV1, and these mice developed PIN with high penetrance [98, 99]. Mixed results have been reported for mice overexpressing truncated ERG. Some studies showed that *ARR2Pb-ERG* mice displayed phenotypes ranging from PIN to adenocarcinoma at old age, with higher levels of ERG expression correlating with more severe phenotypes [100, 101]. Mechanistically, ERG was suggested to activate the YAP1/Hippo transcriptional program, and a mouse model with prostate-specific activation of YAP1 developed phenotypes that were similar to *ARR2Pb-ERG* mice [101]. However, others reported largely normal prostate morphology for the *ARR2Pb-ERG* model [102, 103], the *Pb-Cre; R26*$^{ERG/ERG}$ conditional expression model [104], and models in which the TMPRSS2-ERG fusion product is expressed [105-107]. Mouse strains, timing of analyses, the precise portion of the expressed protein, and transgene integration sites are all possible factors contributing to these varied outcomes. Rigorous quantitation of ERG levels and better control for mouse genetic background may help clarify, but TMPRSS2-ETS fusions certainly need to cooperate with other pathways for PCa to progress. Analysis of genetic alterations in human PCa showed that ERG rearrangement was significantly associated with PTEN loss [103, 106, 108]. Compound mouse models with ERG overexpression and Pten loss, such as *ARR2Pb-ERG; Pten+/-* [103], *ARR2Pb-TMPRSS2-ERG; Pten+/-* [106], *TMPRSS2-ERG knock-in; Pten-/+* and *TMPRSS2-ERG knock-in; Pb-Cre; Pten*$^{fl/fl}$ [105], and *Pb-Cre; Pten*$^{fl/fl}$*; R26*$^{ERG/ERG}$ [104] mice, all showed accelerated PIN and adenocarcinomas progression compared to *Pten*-mutant mice, suggesting synergy between ERG overexpression and PI3K pathway activation. Mechanistically, ERG may restore AR transcriptional output in the Pten-loss background, and upregulate genes involved in cell migration and angiogenesis [104], but differences in ERG- and ETV1-regulated transcriptional programs have also been reported [105].

Interestingly, TMPRSS2-ERG fusion can be accompanied by the deletion of a highly conserved interstitial region between these two genes [109, 110], raising the possibility that this event may have other oncogenic functions besides ERG overexpression. Indeed, in a recent study comparing two *TMPRSS2-ERG* knock-in models, the model containing the interstitial deletion cooperated more strongly with Pten-loss [111]. One of the deleted genes is *Ets2*, and *Pb-Cre; Ets2*$^{fl/fl}$*; Pten*$^{fl/fl}$ mice displayed more aggressive phenotypes than *Pb-Cre; Pten*$^{fl/fl}$ mice, suggesting the delete genes may have tumor suppressor functions [111].

SPOP mutations

Recurrent mutations in the gene *SPOP*, which encodes a Cullin-based E3 ubiquitin ligase subunit, are found in ~10% of primary and advanced PCa cases [8, 112]. Interestingly, *SPOP* mutations are mutually exclusive with ETS family gene rearrangements, defining a distinct molecular subtype of PCa [8, 9, 113]. SPOP mutations are significantly enriched in primary tumors [6], indicating that they are early events during PCa development [114].

In a loss-of-function model, *Pb-Cre; Spop*$^{fl/fl}$ mice developed PIN through upregulation of AR and c-Myc [115]. In another model, SPOP-F133V, a common missense mutation found in human PCa, was conditionally overexpressed in *Pb-Cre; R26*$^{SPOP\text{-}F133V}$ mice [116]. Although SPOP-F133V alone was insufficient to drive tumorigenesis, it synergized with Pten loss, through increasing PI3K/mTOR signaling activity and maintaining AR activity against PI3K-mediated feedback inhibition [116], indicating SPOP-F133V has dominant negative function. Notably, there has been some controversy regarding the tumor-suppressing mechanism of SPOP. Some studies reported that SPOP facilitates the ubiquitination and degradation of ERG, but not TMPRSS2-ERG [117, 118]. However, the vast majority of human SPOP-mutant cancers do not express ERG, and *Pb-Cre; Pten*$^{fl/fl \text{ or } +/+}$*; R26*$^{SPOP\text{-}F133V}$ mice showed no evidence of ERG expression [119], questioning such regulation. Analysis of human PCa datasets and zebrafish models of SPOP-F133V sug-

gested that SPOP mutations drive prostate tumorigenesis at least partly through impaired DNA double strand break repair and increased genomic instability [114].

Wnt signaling pathway

The canonical Wnt signaling pathway via nuclear β-catenin regulates numerous processes in animal development, tissue homeostasis, and diseases [120, 121]. A recent integrated analysis of primary and metastatic PCas found that 10% of the cases harbored genomic alterations in the Wnt/β-catenin pathway [6], and Wnt-related alterations are significantly enriched in CRPCs [7, 11].

To investigate the potential role of the canonical Wnt pathway in prostate tumorigenesis, many groups used the *Ctnnb1*$^{L(ex3)/+}$ mouse strain, in which Cre-mediated deletion of the third exon of the β-catenin gene results in a dominant stable protein [122]. Driven by the *MMTV-Cre*, *Nkx3.1-Cre*, *Pb-Cre or p63*$^{CreERT2/+}$, such mouse models developed squamous metaplasia and varied degrees of PIN [123-128]. These phenotypes progressed to adenocarcinoma when β-catenin stabilization is combined with SV40-large T-antigen overexpression [126] or *Pten* deletion [129], suggesting synergy with the p53/Rb and PI3K pathways, respectively. Notably, although β-catenin level seems to increase in *Pb-Cre; Pten*$^{fl/fl}$ tumors, there is no phenotypic difference between *Pb-Cre; Pten*$^{fl/fl}$ and *Pb-Cre; Ctnnb*$^{fl/fl}$*; Pten*$^{fl/fl}$ tumors, suggesting that β-catenin is dispensable for Pten loss-driven PCa [129]. Besides *Ctnnb1*$^{L(ex3)/+}$-based models, adenocarcinomas were also observed in *Pb-Cre; Apc*$^{fl/fl}$ mice where the Wnt pathway negative regulator Apc is inactivated [130], and in *Ubi-Cat* mice where β-catenin is activated through a genetically modified inducible Wnt co-receptor LRP-5 [131]. Taken together, these data imply Wnt/β-catenin pathway as a driving force of prostate tumorigenesis. Further evidence comes from renal-graft studies showing that manipulation of the stromal compartment by overexpressing *Hmga2* or knocking out *Tgfbr2* enhances paracrine Wnt signaling to promote PCa initiation [132, 133]. Despite these progresses, the role of Wnt activation in promoting PCa cell metastasis remains largely elusive. Developing GEMMs that activate Wnt in advanced tumors should shed light onto this important question.

Ras/Raf/MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) cascade relays extracellular cues to activate Ras and Raf for subsequent phosphorylation and activation of MEK1/2 and ERK1/2 (MAPKs), which phosphorylate multiple targets regulating cell survival, proliferation, and differentiation [134]. Although *RAS* and *RAF* mutations are not frequent in PCa, the activity of the MAPK signaling pathway is often upregulated in both primary and metastatic PCas [9, 10, 135]. Ras^{G12V} and BRaf^{V600E} activating mutations are common in human cancers and are also present in PCa patients [10]. To model these oncogenic events in vivo, *Pb-H-Ras*^{G12V} transgenic mice [136] and *Pb-Cre; K-Ras*$^{LSL-V12/+}$ conditional activating mice [127] were developed, and both models exhibited low grade PIN. In the iBRAF* model where BRaf^{V600E} expression is doxycycline-inducible under the *Ink4a/Arf-/-* background, mice developed prostate adenocarcinomas [137]. Another hotspot mutation, K-Ras^{G12D}, is not found in human PCa. Nevertheless, it has been modeled in *Pb-Cre; K-Ras*$^{LSL-G12D/+}$ mice, which showed no sign of cancer development [138].

Aberrant Wnt signaling has been shown to synergize with Ras/Raf/MAPK activation, as *Pb-Cre; ctnnb1*$^{+/lox(ex3)}$*; K-Ras*$^{LSL-V12/+}$ mice developed invasive carcinoma [127]. But it is the cooperation of the PI3K and MAPK pathway activations in PCa progression that has been best characterized [139, 140]. For example, PCa in *Pb-Cre; Pten*$^{fl/fl}$*; K-Ras*$^{LSL-G12D/+}$ mice displayed epithelial to mesenchymal transition (EMT) and metastatic phenotypes [138, 141], which could be suppressed by inhibition of the chromatin remodeling protein HMGA2 [142]. Metastasis also occurred in *Nkx3.1*$^{CreERT2/+}$*; Pten*$^{fl/fl}$*; K-Ras*$^{LSL-G12D/+}$ mice, and the ETS transcription factor family member Etv4 was activated in response to activation of MAPK and PI3K pathways to promote this process [143]. Importantly, inhibition of mTOR by the drug RAD001 activates the MAPK pathway in both human samples and the *Pb-Cre; Pten*$^{fl/fl}$ model, suggesting a feedback loop between PI3K and MAPK pathways [144]. Recently, loss of Pml in *Pten*-null mouse tumors was shown to relieve this feedback inhibition and activate the MAPK pathway, resulting in an SREBP-dependent lipogenic program to promote metastasis [145]. Collectively, these studies suggest the combined therapy using both mTOR and

MAPK inhibitors as a potential strategy for treating patients with advanced PCa.

FGF/FGFR signaling pathway

The fibroblast growth factor (FGF) and its receptor FGFR are one of the key stromal paracrine signals that regulate prostate epithelial development and homeostasis. The pathway consists of 18 FGF ligands, 4 receptor tyrosine kinases (FGFRs), and a pool of heparan sulfate proteoglycans (HSPGs) [146]. Although genomic mutations in the FGF pathway are rare in human PCa, research using xenograft and cell line models has suggested the existence of abnormal autocrine and paracrine FGF loops in PCa [147]. For instance, enhancing paracrine FGF10 in urogenital sinus mesenchyme led to the formation of PIN and adenocarcinoma [60, 148-151].

In earlier GEM models, FGF7 or FGF8 expression driven by the probasin promoter induced PIN formation [152, 153], while enforced expression of a dominant negative FGFR2iiib induced hyperplasia with neuroendocrine feature [152]. PIN was also observed when FGFR1 or its mutant activated form was overexpressed using the probasin promoter [154-157], and combined expression of FGFR1 and FGFR2iib synergistically promoted high-grade PIN [155]. These models clearly demonstrated that aberrant FGF signaling environment is conducive to PCa initiation. Possible mechanisms include the activation of downstream MAPK/Erk signaling [156], increase in EMT-associated Sox9 and changes in the Wnt signaling pathway [157].

Synergy of FGF signaling with the PI3K pathway was shown in *ARR2PB-Fgf8b; Pb-Cre; Pten*$^{fl/+}$ mice, which developed metastatic PCa [158]. Induced FGFR1 expression also synergized with induced β-catenin expression to accelerate PCa progression, potentially through elevating stromal TGF-β signaling [159]. Recently, a molecular study in human PCa cells and xenografts discovered that FGF signaling was able to sustain a portion of AR-null CRPC [160]. It will be interesting to develop new preclinical GEMMs to test the possibility that inhibition of FGF and MAPK pathways together may be efficacious against PCas that are resistant to AR-directed therapies.

Tp53 and Rb pathways

The p53 and Rb pathways are almost universally involved in cancer [161]. The p53 pathway responds to stresses to initiates programs of cell cycle arrest, cellular senescence or apoptosis [162]. Pathological analyses of clinical samples indicated that *TP53* alterations are closely associated with PCa progression and occur mostly at later stages [163-167]. Comprehensive molecular analyses also showed that *TP53* mutations are highly enriched in metastatic PCa compared to primary PCa [9, 11].

It is important to point out that p53 mutations can provoke activities involved in cell invasion, metastasis, proliferation and survival that are different to those resulting from simply loss of wild-type p53 [168]. Therefore, different p53 mouse models may yield different phenotypes. Simple prostate-specific knockout of p53 in *Pb-Cre; p53*$^{fl/fl}$ mice largely had no tumorigenic effect [43, 76, 169], while overexpressing a human hotspot mutant R273H (mouse R270H) in *Pb-p53*^{R273H} mice [170] or *Nkx3.1-Cre; p53*$^{LSL\text{-}R270H/R270H}$ mice [171] induced PIN. More mouse models have focused on how p53 alterations drive cancer progression. It has been proposed that p53 presents a PCa progression barrier and its alterations lead to genomic instability and evasion of senescence or apoptosis in clones that will become aggressive [65]. In support of this idea, p53-dependent cellular senescence and castration-induced apoptosis were found to be bypassed in *Pb-Cre; Pten*$^{fl/fl}$*; p53*$^{fl/fl}$ mice [43, 50], and analyzing *Pb-Cre; Z-Myc; Pten*$^{fl/fl}$*; p53*$^{fl/fl}$ mice revealed that c-Myc expression shifted the p53 response from senescence to apoptosis by repressing the p53 target gene *p21*^{Cip1} [72, 76]. Other potential oncogenic mechanisms induced by p53 loss include upregulation of hexokinase 2-mediated Warburg effect [172] as well as increased immune cell infiltration through CXCL17 upregulation [51]. Therefore, p53 serves as an essential checkpoint preventing Pten-loss-induced PCa progression.

The tumor suppressor gene Rb plays a pivotal role in cell-cycle regulation. It often undergoes copy number loss in both localized and advanced PCas [10, 11, 173, 174], but is more commonly mutated in neuroendocrine prosta-

te cancers [175]. Prostate-specific deletion of Rb alone in *Pb-Cre; Rb*$^{fl/fl}$ mice only showed hyperplasia [176]. However, it is the NEPC phenotypes induced by the combined loss of Rb and p53 that should be brought to attention. The pioneer models of PCa, including the TRAMP model [177, 178] and the LADY model [179] used the *Pb* promoter to drive the expression of SV40 large T-antigen, which binds and inactivates p53 and Rb [180-182]. These mice showed rapid PCa progression with metastasis, and tumors often had "small cell" and synaptophysin positive phenotypes, suggesting they were neuroendocrine [183, 184]. Carcinomas from the conditional double knockout model *Pb-Cre; p53*$^{fl/fl}$*; Rb*$^{fl/fl}$ also displayed neuroendocrine differentiation [169, 185]. Recently, two important studies characterizing the *Pb-Cre; Pten*$^{fl/fl}$*; Rb1*$^{fl/fl}$ and *Pb-Cre; Pten*$^{fl/fl}$*; Rb1*$^{fl/fl}$*; p53*$^{fl/fl}$ mice suggested that Rb and p53 loss depresses epigenetic reprogramming factors Ezh2 and Sox2, thereby facilitating lineage plasticity and metastasis of prostate adenocarcinoma initiated by *Pten* loss [186, 187]. These findings have important therapeutic implications, since tumors cells can acquire lineage plasticity as a means to escape luminal-targeted androgen deprivation therapy, and epigenetic modulations such as Ezh2 inhibition may provide new approaches to treat NEPC.

AR signaling pathway

The androgen receptor (AR), a member of the steroid hormone receptor superfamily, is essential for normal prostate development, and supports growth of PCa. In the past decade, aberrant AR signaling has emerged as the central driver of CRPC [3]. Alterations of the AR signaling through AR gene mutations, gene/enhancer copy-number amplification, AR splicing variants, and mutations of AR binding partners are particularly frequent in CRPC [7, 9-11, 188, 189].

GEMMs of prostate AR loss- or gain-of-function experiments are generally in agreement with human sequencing data, showing that manipulation of AR signaling alone has subdued effect on early cancer initiation. In the *Pb-mAR* transgenic model where the *AR* transgene is driven by the rat probasin promoter, PIN lesions only appeared in old mice (> 1 year) [190]. PIN was also observed in an *Osr1-Cre* induced AR-overexpressing mouse model [191]. In another study, overexpressing either wild-type AR or AR-T857A (human T877A), an AR mutant present in LNCaP cells that is responsive to non-classical ligands, had no obvious phenotypes, while overexpressing AR-E231G, a mutant with increased ligand-independent activity, induced PCa formation [192]. However, it should be noted that AR-E231G was discovered in the TRAMP model [193], and has not been observed in human PCa. Recently, an AR^{v567es} splice variant frequently found in human CRPC was shown to induce invasive adenocarcinoma in *Pb-AR*^{v567es} transgenic mice by one year of age [194], and overexpression of AR-V7, a constitutively active and androgen-independent AR splice variant, by the *ARR2PB* promoter induced PIN in mice [195]. These models offer opportunities for studying the mechanisms of AR-variant-driven PCa progression. Notably, in these studies AR overexpression started at the developmental stage, and the probasin promoter itself is regulated by androgen. Modeling AR overexpression in later cancer stages may prove to be beneficial.

On the other hand, AR loss-of-function modeling has also been performed by *AR*-floxed conditional knockout using various Cre or CreER lines targeting the whole prostate or specific epithelial or stromal cell types [196-205]. The phenotypes were mixed and sometimes controversial, possibly due to the complex timing and spatial specificities of different Cre expression. Overall, although decreased androgen levels in aging men has been shown to correlate with the increase of PCa incidence [206], the *AR* gene is not lost in human PCa. Therefore, while these loss-of-function models have shed light onto prostate development and normal homeostasis, their cancer-relevance is less clear.

The interplay of AR signaling with other pathways in PCa progression has been under extensive investigation. In renal-graft experiments, overexpression of AR synergized with Akt, K-ras, FGF10, ERG, Src family kinases, and Hmga2 to promote PCa initiation and progression [60, 61, 132, 149, 207-211]. In GEMMs, the PI3K pathway and AR signaling pathway have been shown to form a reciprocal negative feedback loop to drive PCa survival. In *Pb-Cre; Pten*$^{fl/fl}$ mice and human PCa cells, drug inhibi-

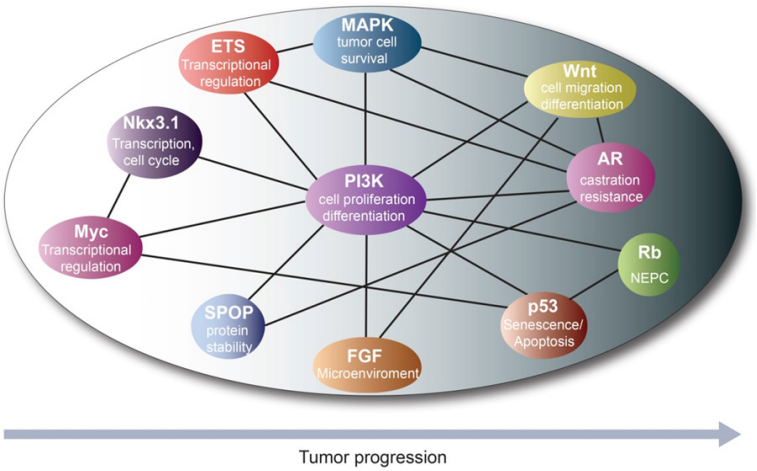

Figure 3. Using GEMMs to study pathway interactions in PCa progression. Diagram summarizes pathway interactions shown to promote PCa progression by studying GEMMs. The PI3K pathway activation has been the most extensively modeled event in PCa GEMMs and usually serves as a baseline model. Cooperation of PI3K pathway with other pathways is required for PCa to overcome various barriers and checkpoints to progress. Each line connecting two pathways indicates that at least one GEMM has been used to establish a functional correlation of the two pathways, through analyzing either phenotypes of double mutant mice or pathway activities in single mutant mice. Pathway interactions revealed by cancer cell line and xenograft studies are not drawn.

tion of the PI3K pathway activates the AR signaling output through increased HER3 kinase expression [212]. *Pb-Cre; Pten*$^{fl/fl}$ tumors were also shown to suppress androgen-responsive genes by upregulating AR signaling co-regulators EGR1, c-JUN, and EZH2, thereby rendering cancer cells less dependent on androgen [213]. On the other side, while AR is dispensable for tumor formation in *Pb-Cre; Pten*$^{fl/fl}$*; AR*$^{fl/Y}$ mice, deletion of *AR* or AR blockade upregulated Akt Activity in *Pten*-null cells by decreasing FKBP5- and PHLPP-mediated Akt dephosphorylation [212, 213]. These findings were also corroborated by models using the *Osr1-Cre* and basal- and luminal-specific CreER lines [204, 214]. Together, these studies provide strong rationale for combined therapy inhibiting both the PI3K and AR signaling pathways in PCa patients. Recently, AR overexpression was shown to accelerate PCa progression in *Pb-Cre* or *p63*$^{CreERT2/+}$ driven *Ctnnb1*$^{L(ex3)/+}$*; R26hAR*$^{L/+}$ mice, where β-catenin was stabilized to activate the Wnt signaling pathway [128, 215]. In these Wnt and AR compound mice, tumor- and metastasis-promoting genes such as Spp1, Egr1, c-Myc, and Sp6 were upregulated. Future GEMMs that turn on AR signaling at later stages in combination with multiple other pathway perturbations should continue to reveal the key to castration resistance in CRPC.

Conclusion

Development of the transgenic, knock-out/in, and Cre-lox conditional expression techniques in mice paved the way for building GEMMs for answering key biological questions in PCa progression. The intact tumor microenvironment and fully functional immune system in GEMMs offer unique advantages to other experimental models. Although mice rarely develop spontaneous PCa, modeling the recurrent genetic alterations of human patients has provided a much clearer picture of PCa progression. It is increasingly appreciated that many of the molecular events, such as p53 or Rb loss of function and *TMPRSS2-ERG* fusion, are insufficient to initiate PCa if they occur early individually. However, these events may prime prostate cells for future oncogenic transformation by altering their downstream transcriptional programs. PI3K pathway activation in the form of *Pten* loss, on the other hand, has proved to be an essential step in many models for the transition from PIN to adenocarcinoma. Further progression to CRPC appears to require PI3K signaling cooperation with other pathways (**Figure 3**). For example, the discovery of the reciprocal negative feedback loop between PI3K and AR signaling argues for the combined treatment targeting both pathways. The finding that loss of p53 and Rb at later stage further drives the tumor cells to undergo lineage switch provides new potential therapeutic avenues to inhibit disease progression towards neuroendocrine cancer. In comparing various GEMM studies, it is important to bear in mind that mouse strain background could be a complicating factor contributing to some of the controversies. For example, mice of the commonly used C57BL/6 genetic background are relatively tumor resistant [216]. PCa metastasis remains an underaddressed topic in GEMMs, as very few models show bone me-

tastasis, which is common in patients. While this may very well reflect intrinsic species differences, developing new models, such as late-stage activation of Wnt and AR variants models, may lead to new discoveries on the mechanisms of PCa metastasis. With the incorporation of new technologies such as CRISPR and single cell technqiues, we envision that the next-generation mouse models will help dissect the signaling cross talks in PCa with more sophisticated modeling of molecular events in more refined tissue space.

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None.

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