PTEN Mouse Models of Cancer Initiation and Progression

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Phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) is one of the most frequently mutated, deleted, and functionally inactivated tumor suppressor genes in human cancer. *PTEN* is found mutated both somatically and in the germline of patients with PTEN hamartoma tumor syndrome (PHTS). *PTEN* encodes a dual lipid and protein phosphatase that dephosphorylates the lipid phosphatidylinositol-3,4,5-trisphosphate (PIP₃), in turn negatively regulating the oncogenic PI3K-AKT pathway, a key proto-oncogenic player in cancer development and progression. Because of importance of PTEN in tumorigenesis, a large number of sophisticated genetically engineered mouse models (GEMMs) has been designed to elucidate the underlying mechanisms by which the “PTEN pathway” promotes tumorigenesis, while simultaneously providing a well-tailored system for the identification of novel therapies and offering platforms for new drug discoveries. This review summarizes the major cancer mouse models through which the PTEN pathway has been genetically deconstructed, and outlines the rapid development of GEMMs toward more detailed functional and tissue-specific analysis.

Phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) is frequently somatically mutated or deleted in human cancers. In 1997, genetic studies first identified PTEN as a putative tumor suppressor (Li et al. 1997; Teng et al. 1997), and the importance of *PTEN* in tumor suppression was soon reaffirmed by the identification of germline *PTEN* mutations in PTEN hamartoma tumor syndrome (PHTS), including mutation positive subsets of Cowden syndrome (OMIM ID: 158350), Bannayan-Riley-Ruvalcaba syndrome (OMIM ID: 158350), Proteus syndrome (OMIM ID: 176920), and Proteus-like syndrome (Arch et al. 1997; Liaw

et al. 1997; Zhou et al. 2001). Genetic inactivation of *Pten* in mice demonstrated its tumor-suppressive role in multiple tumors of various origins, and suggested the haploinsufficiency of PTEN in terms of tumor suppression in some tissue types (Di Cristofano et al. 1998, 1999; Suzuki et al. 1998; Podsypanina et al. 1999). Moreover, partial loss of PTEN function was found to be sufficient to trigger some cancer types, while a reduction of PTEN levels below 50% increased tumor progression in some human tissues and genetically engineered mouse models (GEMMs). These observations suggest that a continuum rather than a stepwise model

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of PTEN activity best describes the process triggering tumor initiation and progression (Alimonti et al. 2010a; Berger et al. 2011).

PTEN is a dual-specificity protein and lipid phosphatase, and its primary substrate is the second messenger phosphatidylinositol 3,4,5-triphosphate (PIP₃), which is hydrolyzed to phosphatidylinositol 4,5-bisphosphate (PIP₂) by PTEN lipid phosphatase activity (Song et al. 2012; Lee et al. 2018). PTEN suppresses the phosphatidylinositol 3-kinase (PI3K) pathway by inhibiting membrane recruitment and activation of the oncogenic AKT in a PIP₃-dependent manner, thereby inhibiting cell proliferation, growth, and survival. Accordingly, PTEN has emerged as a crucial node in a wide range of cancer therapies (Song et al. 2012; Lee et al. 2018).

PTEN is strictly regulated, and its deregulation through aberrant subcellular localization or posttranslational modifications (or both) occurs frequently in tumorigenesis (Lee et al. 2018). Mechanistically, monoubiquitination or sumoylation regulates the import of PTEN into the nucleus where it functions as a scaffold and exerts PIP₃-independent functions in genomic integrity, induction of apoptosis, cell-cycle control, and senescence (Trotman et al. 2007; Salmena et al. 2008; Song et al. 2012; Bassi et al. 2013; Lee et al. 2018). In the cytoplasm, scaffolding by PTEN regulates not only the activity of inositol 1,4,5-triphosphate receptors (IP₃Rs), and consequently, Ca²⁺-mediated apoptosis, but also the activation of the oncogenic tumor necrosis factor (TNF)-nuclear factor κ B (NF- κ B) pathway (Kuchay et al. 2017; Zhao et al. 2017). Intriguingly, a recent study found that PTEN also exists as a dimer, and that dimer formation and recruitment at the plasma membrane are crucial for PTEN activation and function (Papa et al. 2014). Moreover, through combined biochemical and genetic approaches, it was also demonstrated that the HECT-type WWP1 specifically triggers atypical nondegradative polyubiquitination of PTEN to suppress its dimerization, membrane recruitment, and tumor-suppressive functions both in vitro and in vivo (Lee et al. 2019). Importantly, both genetic ablation and pharmacological inhibition of

WWP1 were found to trigger PTEN reactivation to unleash its tumor-suppressive activity. These recent discoveries offer hope that the elucidation of the mechanisms controlling PTEN protein levels and activity will open new therapeutic avenues for cancer prevention and treatment through restoration of the protein's tumor-suppressive activity.

OVERVIEW OF GENETICALLY ENGINEERED *Pten* MOUSE MODELS

Genetically engineered *Pten* mouse models have multiplied in number over the past 20 years, but can generally be classified into three distinct groups according to the level of PTEN manipulation and the specifics of their outcomes or goals. These models include (1) down-regulation of PTEN, either alone or in combination with loss-of-function of another tumor suppressor or gain-of-function of an oncogene to accelerate cancer progression; (2) elevation of PTEN expression and function; and (3) mouse models of cancer-associated *PTEN* mutations. The most relevant *Pten* mouse models are schematically shown in Figure 1 and described below.

Down-Regulation of PTEN, Either Alone or in Combination with Loss-of-Function of Another Tumor Suppressor or Gain-of-Function of an Oncogene to Accelerate Cancer Progression

This group of models can be divided into several subgroups.

Whole-Body Manipulation of *Pten*

The earliest GEMMs were developed soon after the identification of *PTEN* as a candidate tumor suppressor gene (Di Cristofano et al. 1998; Suzuki et al. 1998; Podsypanina et al. 1999). The first *Pten* homozygous knockout mice proved embryonically lethal at days 3.5–9.5 (Di Cristofano et al. 1998), but heterozygous *Pten*^{+/-} mice survived to maturity, and developed a broad range of neoplastic lesions, including prostate intraepithelial neoplasia (PIN), lymphomas, dysplastic intestinal polyps, and endometrial complex atypical

Figure 1. Genetically engineered *Pten* mouse models. Genetically engineered *Pten* mouse models can be classified into six distinct groups. These include (1) whole-body knockout of *Pten*; (2) generation of hypomorphic *Pten* model by targeting intron 3 of *Pten* with a cytomegalovirus (CMV) promoter-driven neomycin (*neo*) cassette, which reduced PTEN expression to 80%. These *Pten*^{hy/+} mice were then crossed with *Pten*^{+/-} mice to generate hypomorphic mouse cohorts with decreasing levels of PTEN expression ($Pten^{+/+} > Pten^{hy/+} > Pten^{+/-} > Pten^{hy/-}$); (3) tissue-specific deletion of *Pten*; (4) compound mouse models: combined *Pten* deletion along with another tumor suppressor or oncogene; (5) elevation of PTEN expression or function through bacterial artificial chromosome (BAC) technology of additional copies of the *Pten* locus; and (6) modeling cancer-associated *Pten* mutations in mice through knockin and CRISPR technology.

hyperplasia (Di Cristofano et al. 1998; Suzuki et al. 1998; Podsypanina et al. 1999). Some of these lesions, such as intestinal polyps and endometrial hyperplasia, are also observed in human Cowden syndrome (Arch et al. 1997; Liaw et al. 1997; Zhou et al. 2001).

Hypomorphic *Pten* Mouse Model

It has been hypothesized that subtle variations in the tumor suppressor gene adenomatous polyposis coli (*APC*) levels can promote colon cancer development (Yan et al. 2002). To explore this hypothesis in the context of *PTEN*

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biology, the Pandolfi Laboratory generated a *Pten* hypomorphic mouse model (*Pten*^{hy/+}) by targeting intron 3 of *Pten* with a neomycin (*neo*) cassette, under the control of a cytomegalovirus (CMV) promoter, which in turn led to transcriptional interference and subsequently reduced PTEN expression to 80% of its normal baseline level. These *Pten*^{hy/+} mice were then crossed with *Pten*^{+/-} mice to generate hypomorphic mouse cohorts with decreasing levels of PTEN expression (*Pten*^{+/+} > *Pten*^{hy/+} > *Pten*^{+/-} > *Pten*^{hy/-}). *Pten*^{hy/+} mice developed a spectrum of neoplastic lesions (mammary tumors, uterine tumors, lymphadenopathy, intestinal polyps, and pheochromocytoma), with breast tumors present with the highest penetrance. All breast tumors analyzed in these cohorts retained two intact copies of *Pten* and maintained PTEN levels above heterozygosity (Alimonti et al. 2010a). Reduction in PTEN levels below 50% further accelerated prostate cancer progression (Trotman et al. 2003), suggesting that the process of tumor development is governed by a continuum model of PTEN tumor suppression rather than stepwise alteration of PTEN levels (Fig. 2; Berger et al. 2011).

Tissue-Specific Deletion of *Pten*

LoxP/CRE technology has enabled the generation of tissue-specific PTEN deletion models, which have resulted in tumor development specifically in those tissues subject to loss of PTEN expression (Table 1), while also yielding a number of unexpected biological outcomes (Kishimoto et al. 2003; Andres-Pons et al. 2007; Renner et al. 2008; Renner and Carnero 2009; Inoue et al. 2013):

Complete Loss of *Pten* in the Prostate Triggers Cellular Senescence, a Potent Fail-Safe Mechanism to Suppress Tumor Growth in Prostate Cancers

Mouse model studies have revealed the crucial roles of PTEN in prostate cancer (Civenni et al. 2018). Although partial loss of *Pten* increases cellular growth and proliferation (Trotman et al. 2003; Alimonti et al. 2010a; Berger et al.

Figure 2. Tissue specificity and context dependency of phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) tumor suppression. The phenotypic outcome of reduction in PTEN expression is differentially manifested depending on tissue type and genetic background. The effect of complete loss of *PTEN* is highly context-dependent because of the obligate haploinsufficiency caused by *PTEN*-loss-induced cellular senescence (PICS). (From Berger et al. 2011; adapted, with permission, from Springer Nature © 2011.)

2011), complete loss of *Pten* in the prostate epithelium results in cellular senescence (Chen et al. 2005; Alimonti et al. 2010b), which functions as a fail-safe mechanism that restricts tumor progression. These data explain why complete loss of *Pten* alone in the mouse prostate results in indolent tumors with minimally invasive features after a long latency, and why complete loss of *Pten* is not frequently observed during cancer initiation. *Pten* loss can be prevalent, however, in metastatic and advanced prostate cancer, where the pathways responsible for senescence are frequently dysregulated. Mechanistic studies have revealed that *PTEN*-loss-induced cellular senescence (PICS) can be attributed to the up-regulation of both p53 and p16 (Chen et al. 2005; Alimonti et al. 2010b; Song et al. 2011).

Table 1. Tissue-specific *Pten* deletion and biological outcomes

Tissue-specific deletion of <i>Pten</i>	Phenotype
Mammary-specific knockout	Proliferation and dysplasia
Hepatocyte-specific knockout	Hepatocellular carcinoma and steatohepatitis
T-cell-specific knockout	Defects in central and peripheral tolerance
Prostate-specific knockout	Senescence

Mammary-Specific Deletion of *Pten* Increases Proliferation and Dysplasia

Conditional knockout of *Pten* in the mammary gland was found to lead to increased intraluminal focal hyperplasia and early development of mammary tumors, a consequence of the loss of *Pten* function in controlling the proliferation, differentiation, and apoptosis of mammary epithelial cells (Li et al. 2002).

Hepatocyte-Specific *Pten* Deficiency Leads to Hepatocellular Carcinomas and Steatohepatitis

PTEN expression is reduced or absent in ~50% of hepatoma patients, and hepatocyte-specific deletion of *Pten* (*Albumin Cre; Pten^{fl/fl}*) in mice leads to steatohepatitis with triglyceride accumulation and hepatomegaly (Horie et al. 2004). Furthermore, loss of *Pten* in the liver also triggered liver cell adenomas in 47% of mice by 44 weeks of age, while 100% of mice livers examined exhibited insulin hypersensitivity. Mechanistically, *Pten* knockout hepatocytes were not only hyperproliferative, with higher phosphorylation of AKT and ERK but also displayed elevated levels of PPAR γ and SREBP1c. Recently, new transformative approaches have been implemented to rapidly generate cancer models in mice by using CRISPR technology (Xue et al. 2014; Wang et al. 2015). Both hydrodynamic injection and adenoassociated virus (AAV)-mediated delivery methods of plasmid DNA expressing Cas9 and *Pten* targeting

sgRNA to the liver increased AKT activation, resulting in steatohepatitis and hepatomegaly phenotypes in mouse livers, phenocopying the effects of *Pten* deletion in mice by using LoxP/Cre technology. These data provide evidence of the crucial roles played by PTEN in regulating hepatocyte homeostasis, glucose metabolism, lipogenesis, and tumorigenesis (Horie et al. 2004).

T-cell-Specific Deletion of *Pten* Results in Defects in Central and Peripheral Tolerance

Pten-deficient T cells were hyperproliferative, resistant to apoptosis, and exhibited increased phosphorylation of AKT and ERK, which led to elevated levels of B cells and CD4⁺ T cells in the periphery, as well as spontaneous activation of CD4⁺ T cells, autoantibody production, and hypergammaglobulinemia. Moreover, these mice showed increased thymic cellularity, in part as a result of a defect in thymic negative selection. A study of this model found that all mice developed CD4⁺ T-cell lymphomas by 17 weeks of age (Suzuki et al. 2001). Similar immune-related disorders were also found in *Pten* heterozygous (*Pten^{+/-}*) mice. These mice developed a lethal polyclonal autoimmune disorder with features reminiscent of those observed in *Fas*-deficient mutants. Mechanistically, Fas-mediated apoptosis was impaired in *Pten^{+/-}* mice, and T lymphocytes from these mice showed reduced activation-induced cell death and increased proliferation upon activation (Di Cristofano et al. 1999). These results demonstrate the crucial roles of PTEN in maintaining immune response homeostasis.

Combination of *Pten* Loss with Either Loss-of-Function of a Tumor Suppressor or Gain-of-Function of an Oncogene

Given the impact of *PTEN* loss in tumorigenesis, a strategy was soon designed to unravel the specific pathway(s) and the underlying mechanisms involved in *PTEN* loss triggered advanced cancer progression (Table 2). To this end, *Pten^{+/-}* mice were bred with *Cdkn1b* (encoding p27^{kip1})^{-/-} mice. Indeed, the concomi-

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Table 2. Selected genetically engineered *Pten* mouse models in cancer initiation and progression

Genotype	Phenotype
<i>Pten</i> ^{+/-} ; <i>Cdkn1b</i> ^{+/-} or <i>Pten</i> ^{+/-} ; <i>Cdkn1b</i> ^{-/-}	Accelerates spontaneous neoplastic transformation and incidence of prostate intraepithelial neoplasia (PIN) development
<i>Pten</i> ^{+/-} ; <i>Nkx3.1</i> ^{+/-} or <i>Pten</i> ^{+/-} ; <i>Nkx3.1</i> ^{-/-}	Increases the progression from PIN to high-grade PIN or early carcinoma
<i>Pten</i> ^{+/-} ; <i>Tsc2</i> ^{+/-} or <i>Pten</i> ^{+/-} ; <i>Tsc2</i> ^{-/-}	Increases the progression from PIN to prostate cancer
<i>Nkx3.1</i> ^{CreERT2/+} ; <i>Pten</i> ^{fx/fx} ; <i>KRas</i> ^{G12D/WT} or <i>Nkx3.1</i> ^{CreERT2/+} ; <i>Pten</i> ^{fx/fx} ; <i>KRas</i> ^{LSL-G12D/WT}	Accelerates cancer progression, accompanied by epithelial-to-mesenchymal transition (EMT) and macrometastasis to lung and liver
Hb13-Myc; Hb13 ^{Cre} <i>Pten</i> ^{fx/fx}	Develops lethal adenocarcinoma with distant metastases
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Fgf8b</i>	Develops prostatic adenocarcinoma with readily detectable lymph node metastasis
Pb ^{Cre} ; ERG; <i>Pten</i> ^{+/-} or <i>Pten</i> ^{fx/fx} ; R26 ^{ERG}	Increases high-grade PIN to prostatic invasive adenocarcinoma
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Sox9</i>	Promotes proliferation and cooperates with <i>Pten</i> loss to trigger tumor formation
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Her2</i>	Develops aggressive prostate cancers
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Notch</i>	Promotes EMT and FOXC2-dependent metastases
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Bmi1</i>	Develops invasive adenocarcinoma
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>p53</i> ^{fx/fx}	Overcomes <i>Pten</i> -loss-induced senescence and develops invasive adenocarcinoma
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Smad4</i> ^{fx/fx}	Develops aggressive prostate cancer with metastasis to lymph nodes and lungs
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>p53</i> ^{fx/fx} ; <i>Smad4</i> ^{fx/fx} or Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Smad4</i> ^{fx/fx} ; <i>mTert</i>	Increases prostate cancer progression with bone metastasis
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Gata3</i> ^{fx/fx}	Increases tumor progression and invasion
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Zbtb7a</i> ^{fx/fx}	Accelerates prostate cancer progression with bypass of <i>Pten</i> -loss-induced senescence
Pb ^{Cre} ; <i>Pten</i> ^{fx/fx} ; <i>Pml</i> ^{fx/fx}	Develops lethal and metastatic prostate cancer

tant inactivation of one allele of *Pten* and one or both *cdkn1b* alleles accelerated spontaneous neoplastic transformation and PIN development around 13–22 weeks with 100% penetrance (Di Cristofano et al. 2001). Similarly, crossing *Nkx3.1*^{-/-}, lacking a transcriptional factor that plays an important role in prostate development and tumorigenesis, and *Pten*^{+/-} mice increased progression from PIN to high-grade PIN with 60% penetrance in 26 weeks or early carcinoma with 100% penetrance in 52 weeks (Kim et al. 2002). These mice even exhibited invasive carcinoma once they had reached 1 year of age (Abate-Shen et al. 2003). Interestingly, genetic analysis of *Pten* and *Tsc2* functional interactions revealed asymmetrical haploinsufficiency in tumor suppression. Both *Pten* and *Tsc2* were haploinsufficient for suppression of tumorigenesis initiated by *Pten* het-

erozygosity (e.g., PIN), while neither *Pten* nor *Tsc2* were found to be haploinsufficient for repression of carcinogenesis arising from *Tsc2* heterozygosity (e.g., renal cancer), providing a rationale for the asymmetrical haploinsufficiency of *Pten* or *Tsc2* in tumor suppression (Ma et al. 2005). The insights gleaned from these studies have spurred scientists to continue to take advantage of tissue-specific conditional knockout of *Pten* to further explore the crucial and context-dependent roles of PTEN in tumorigenesis.

Conditional *Pten* knockout mice have also been crossed with mice expressing either gain-of-function oncogenes or loss-of-function tumor-suppressive genes. For example, when *Nkx3.1*^{Cre;ER(T2)+}; *Pten*^{flox/flox} mice were crossed with *lox-stop-lox BrafV600E* mice, the resulting hybrids developed lethal prostate tumors that were resistant to castration and metastasized

to the lymph nodes and lungs in ~30% of cases (Wang et al. 2012). Moreover, crossing $Nkx3.1^{Cre;ER(T2)+}; Pten^{flox/flox}$ mice with mice expressing constitutively active KRAS ($K-ras^{G12D/WT}$) resulted in accelerated *Pten* loss-driven progression, coupled with epithelial-to-mesenchymal transition (EMT) and macrometastases in the lungs and liver with 100% penetrance, but not bone metastases (Mulholland et al. 2012). Similar results have been observed in $Nkx3.1^{Cre;ER(T2)+}; Pten^{flox/flox}$ mice crossed with a cre-dependent oncogenic KRAS cassette ($Kras^{LSL-G12D/+}$). These mice developed aggressive adenocarcinoma and macrometastasis with 100% penetrance in both lung and liver, with oncogenic *Ets* variant 4 (*Etv4*) up-regulation (Aytes et al. 2013). Likewise, an increase in the penetrance of aggressive prostate cancer was observed when *Pten* loss was combined with another oncogenic stimulus such as MYC (Hubbard et al. 2016), ERG (Carver et al. 2009; Chen et al. 2013), SOX9 (Thomsen et al. 2010), FGF8b (Zhong et al. 2006), HER2 (Ahmad et al. 2011), NOTCH (Kwon et al. 2016), and BMI1 (Nacerdine et al. 2012).

Although PTEN is a crucial suppressor of prostate tumorigenesis, progression from PIN to aggressive adenocarcinoma and castration-resistant prostate cancer (CRPC) was found to require additional genetic perturbations. The tumor suppressor p53 was found to be a strong candidate for these manipulations. Like *PTEN*, *TP53* is among the most commonly somatically inactivated or mutated genes in human cancer, including advanced prostate cancer (Di Cristofano and Pandolfi 2000; Vogelstein et al. 2000; Robinson et al. 2015; Abida et al. 2019). To explore the results of the mutual inactivation of both tumor suppressors, $Pb^{Cre4}; Pten^{flox/flox}$ mice were bred with $p53^{flox/flox}$ mice to generate $Pb^{Cre4}; Pten^{flox/flox}; p53^{flox/flox}$ mice. Surprisingly, conditional inactivation of *Trp53* in the mouse prostate failed to produce a tumor phenotype, while complete *Pten* inactivation in the prostate induced indolent invasive prostate cancer after long latency. However, combined inactivation of *Pten* and *Trp53* in mice led to the development of invasive adenocarcinoma as early as 2 weeks of age, and proved lethal to mice by 7 months of

age. Mechanistically, complete genetic inactivation of *Pten* was shown to trigger a p53-dependent senescence program that restricted tumorigenesis, and was bypassed by compound loss of *Trp53*. These results suggest a model for cooperative tumor suppression in which p53 functions as a potent fail-safe mechanism for *Pten*-deficient tumors (Chen et al. 2005).

Apart from p53 induction, the transforming growth factor β (TGF- β)/*Smad4* tumor-suppressive pathway is also activated in advanced prostate cancer upon loss of PTEN expression. Hence, combined prostate-specific *Pten* and *Smad4* knockout led to the development of aggressive prostate cancer with metastasis to the lymph nodes and lungs (Ding et al. 2011). Further combinations with either overexpression of active telomerase in double *Pten/Trp53* knockout mice or triple knockout of *Pten/Trp53/Smad4* led to bone metastasis (Ding et al. 2012). Among other PTEN-deficient models, prostate-specific knockout of *Gata3* combined with *Pten* loss was shown to increase tumor progression and invasion (Nguyen et al. 2013). Moreover, compound prostate-specific inactivation of zinc finger and BTB-domain-containing protein 7A (*Zbtb7a*), which was genetically lost and down-regulated in a subset of advanced prostate cancers, resulted in a marked acceleration of *Pten*-loss-driven prostate cancer progression through the activation of Sry (sex-determining region Y)-box9 (*Sox9*) oncogenic activity, and further bypass of *Pten*-loss-induced cellular senescence (Wang et al. 2013). Recently *PML* was found to be frequently codeleted with *PTEN* in metastatic prostate cancer, and that combined conditional inactivation of *Pml* in the mouse prostate triggers the transformation of indolent *Pten*-null tumors into lethal and metastatic prostate cancer. Transcriptional profiling analyses of tumors revealed MAPK reactivation and hyperactivation of the prometastatic SREBP transcriptional program (Chen et al. 2018). On this basis, a high-fat diet (HFD) administered to mice was capable of inducing lipid accumulation in prostate tumors, and was shown to be sufficient to trigger metastasis in a nonmetastatic *Pten*-null mouse model (Chen et al. 2018). So far, the discoveries summarized above demon-

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strate the power of GEMMs to deconvolute and reconstruct the genetic makeup and complexity of tissue-specific human cancers, and lay a framework for future drug discovery and therapeutic strategies.

Elevation of PTEN Expression and Function

Partial loss of *PTEN* is known to trigger cancer susceptibility and tumor progression (Di Cristofano et al. 1998; Suzuki et al. 1998; Podsypanina et al. 1999; Song et al. 2012; Lee et al. 2018). Therefore, both elevation of PTEN expression and restoration of PTEN activity hold promise as potential strategies for cancer prevention and therapy. Several transgenic mouse colonies were generated with PTEN expression elevated to varying levels through a bacterial artificial chromosome (BAC)-mediated approach. The resulting “Super PTEN” mice have proved to be viable, despite decreased body size (Garcia-Cao et al. 2012). Importantly, elevated PTEN levels led to increased energy expenditure and reduced glucose and glutamine uptake. On this basis, Super PTEN mice were lean and displayed healthy metabolism. Importantly, mice and cells derived from these mice were resistant to oncogenic transformation, while PTEN elevation also prevented the development of key tumorigenic features, including glutaminolysis and the Warburg effect. These data suggest the possibility of strategic tumor prevention and therapy through pharmacological increase in wild-type PTEN level or function.

In an ongoing effort to explore the potential impact of the restoration and elevation of PTEN function, the Pandolfi Laboratory has also carried out screenings for PTEN negative regulators. Such screenings have identified an HECT domain ubiquitin E3 ligase, WWP1, which specifically triggers PTEN K27-linked polyubiquitination to suppress its dimerization, membrane recruitment, and tumor-suppressive function. Furthermore, WWP1 was found to be transcriptionally activated by the MYC proto-oncogene, while genetic depletion of *Wwp1* in *Myc*-driven mouse models (*Hi-Myc; Wwp1*^{-/-}) of prostate cancer was found to increase PTEN membrane recruitment and tumor-suppressive function,

leading to inhibition of the PI3K-AKT pathway and MYC-driven tumorigenesis (Lee et al. 2019). These findings demonstrate that WWP1 acts downstream of MYC, and that inactivation of *WWP1* can restore and enhance the tumor-suppressive activity of PTEN, paving the way toward a long-sought approach for tumor suppressor reactivation for cancer prevention and treatment.

Mouse Models of Cancer-Associated PTEN Mutations

Beyond frequent *PTEN* somatic mutations in multiple human cancers, germline *PTEN* mutations define a range of tumor syndromes referred to as PHTS, including the *PTEN* mutation positive subset of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (Arch et al. 1997; Liaw et al. 1997; Zhou et al. 2001; Yehia et al. 2019). Indeed, GEMMs with *Pten* mutations have emerged as an effective means of studying the underlying mechanisms and physiological functions by which *PTEN* mutations impact these syndromes. Charis Eng’s group at Cleveland Clinic was the first group to generate germline *Pten* mutations in mice (R233Q; R234Q; K266N; K267Q), which they termed *Pten*^{m3m4} mice for brevity. They generated *Pten*^{m3m4} mice by introducing all these missense mutations into exon 7 of the mouse *Pten* locus. These mutations collectively target the sequences analogous to the third and fourth nuclear localization-like sequences found in the human *PTEN* gene (Chung et al. 2005). Homozygous *Pten*^{m3m4} mice displayed reduced PTEN protein levels and cytoplasmically predominant PTEN, resulting in region-specific increases in brain weight and AKT activation. Importantly, the mice developed macrocephaly, a major component of PHTS, and recapitulated features of high-functioning autism spectrum disorder (ASD) with sex-specific increases in social motivation in male mice, poor balance, and normal recognition memory (Mester et al. 2011; Tilot et al. 2014).

Caserta et al. (2015) generated and characterized a *Pten* knockin mouse model harboring a phenylalanine to valine mutation (*Pten* F341V or *Pten*^{FV} for brevity) in the C2 domain of

PTEN, with the former observed in human cancer. Although homozygous *Pten*^{FV/FV} embryos exhibited reduced levels of PTEN, the cells still had intact AKT signaling, developed normally, and were carried to term. Interestingly, *Pten*^{FV/+} mice developed tumors in the mammary gland, stomach, thymus, and adrenal medulla, but not in the organs that are usually sensitive to *Pten* depletion, including the uterus, prostate, and thyroid glands. This suggests that *Pten*^{F341V} non-catalytic mutation plays an oncogenic function through a different mechanism than canonical activation of AKT signaling, already shown to predispose to cancer development in vivo (Caseria et al. 2015). *Pten* knockin mice harboring two cancer-associated mutations, *Pten*^{C124S} (protein and lipid phosphatase inactive mutant) and *Pten*^{G129E} (lipid phosphatase inactive mutant), were also generated. These models were markedly tumor prone and developed tumors that are more aggressive than those developed by *Pten* heterozygous mutants. Importantly, in the same study, it was also shown that PTEN homodimerizes at the plasma membrane in an active conformation, to exert its lipid phosphatase activity on PIP₃, and that catalytically inactive cancer-associated PTEN mutants can heterodimerize with wild-type PTEN and in doing so, inhibit wild-type PTEN catalytic activity in a dominant negative manner. In line with this, heterozygous *Pten*^{C124S/+} and *Pten*^{G129E/+} tissues also displayed higher levels of PI3K-AKT activation than their wild-type and *Pten*^{+/-} counterparts. In summary, in vivo *Pten* knockin models have revealed that *PTEN* mutations are not always synonymous with *PTEN* loss in terms of their aberrant activity, but may also operate through the deregulation of distinct PTEN mechanisms and molecular functions (Papa et al. 2014).

CONCLUDING REMARKS

Since its discovery as a bona-fide tumor suppressor, numerous in vivo studies have highlighted the variety and importance of PTEN functions, which include inhibition of cellular proliferation, growth and migration, regulation of DNA damage repair, and maintenance of ge-

nomic integrity and tumor-suppressive states. As a result of these critical functions, the outcome of *PTEN* loss proves to be devastating, resulting in the distortion of many pivotal pathways and processes, in turn triggering the dysregulation of embryonic development, cellular homeostasis, and tumorigenesis.

New genetic methods have provided a platform for the study of these effects, and the manipulation of the mouse genome to create multiple mouse colonies designed to decipher specific aspects underlining the biology of cancer initiation and progression. Over time, these GEMMs have yielded a wealth of new data, which have helped us better understand both the cellular and molecular mechanisms involved in tumorigenesis. At first, genetic inactivation of *Pten* was achieved through whole-body knockout technology with lack of tissue specificity and uncontrolled timing of the genetic inactivation of *Pten*. However, the utilization of tissue-specific promoters and Cre-mediated recombination (inducible or not) overcame these problems, and enabled the genetic modification of PTEN in a tissue-specific and temporally controlled manner. These approaches offered researchers the opportunity to study in a detailed manner the role of PTEN deregulation in cancer initiation and progression, as well as in a cellular context-specific manner. Recently, comprehensive genetic manipulation of the mouse genome has expanded to take advantage of CRISPR-mediated approaches, which have made possible new combinations of genetic alterations and a far more sophisticated level of genomic editing.

The extensive functional characterization of the roles of PTEN in tumorigenesis in GEMMs has also suggested multiple new targets for drug development, and further facilitated new methods for cancer prevention and therapy. This holds promise for patients coping not only with tumors driven by aberrant PTEN function, but also with disorders caused by germline *PTEN* mutations.

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