PTEN is among the most commonly lost or mutated tumor suppressor genes in human cancer. PTEN, a bona fide lipid phosphatase that antagonizes the highly oncogenic PI3K-AKT-mTOR pathway, is considered a major dose-dependent tumor suppressor. Although PTEN function can be compromised by genetic mutations in inherited syndromes and cancers, posttranslational modifications of PTEN may also play key roles in the dynamic regulation of its function. Notably, deregulated ubiquitination and deubiquitination lead to detrimental impacts on PTEN levels and subcellular partitioning, promoting tumorigenesis. While PTEN can be targeted by HECT-type E3 ubiquitin ligases for nuclear import and proteasomal degradation, studies have shown that several deubiquitinating enzymes, including HAUSP/USP7, USP10, USP11, USP13, OTUD3 and Ataxin-3, can remove ubiquitin from ubiquitinated PTEN in cancer-specific contexts and thus reverse ubiquitination-mediated PTEN regulation. Researchers continue to reveal the precise molecular mechanisms by which cancer-specific deubiquitinases of PTEN regulate its roles in the pathobiology of cancer, and new methods of pharmacologically for modulating PTEN deubiquitinases are critical areas of investigation for cancer treatment and prevention. Here, we assess the mechanisms and functions of deubiquitination as a recently appreciated mode of PTEN regulation and review the link between deubiquitinases and PTEN reactivation and its implications for therapeutic strategies.

INTRODUCTION

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is one of the most frequently lost or mutated tumor suppressor genes in human cancer. Its encoded protein, PTEN, negatively regulates the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) signaling pathway through dephosphorylation of the plasma membrane lipid phosphoinositide-3,4,5-triphosphate. As a consequence, loss of PTEN function leads to potent derepression of the PI3K-AKT-mTOR pathway, which stimulates cell survival, proliferation, energy metabolism, and architecture. PTEN also shows protein phosphatase, specifically dephosphorylating tyrosine, serine- and threonine-phosphorylated polypeptides in vitro and several different cellular substrates, including focal adhesion kinase (FAK), cAMP-responsive element-binding protein (CREB), tyrosine kinases SRC and PTK6, and insulin receptor substrate 1 (IRS1) and several different cellular substrates, including focal adhesion kinase (FAK), cAMP-responsive element-binding protein (CREB), tyrosine kinases SRC and PTK6, and insulin receptor substrate 1 (IRS1). PTEN also shows protein phosphatase, specifically dephosphorylating tyrosine, serine- and threonine-phosphorylated polypeptides in vitro and several different cellular substrates, including focal adhesion kinase (FAK), cAMP-responsive element-binding protein (CREB), tyrosine kinases SRC and PTK6, and insulin receptor substrate 1 (IRS1). Furthermore, phosphatase-independent activities (mostly scaffolding) of PTEN regulate many processes, such as DNA replication, DNA repair, genomic stabilizing events, and cell cycle progression, have also been identified, implicating the noncanonical roles of PTEN in tumorigenesis. Germline heterozygous pathogenic mutations in PTEN have been described in a variety of rare syndromes with different clinical presentations that are collectively known as PTEN hamartoma tumor syndromes (PHTSs), which exhibit features of both benign and malignant tumors. Many modeling efforts with Pten-knockout mice have demonstrated that PTEN functions in a haplo-insufficient manner; paradoxically, when PTEN levels are nearly completely loss, a strong cellular senescence program is triggered, which is a 'fail-safe' brake on tumor progression. Notably, an analysis of a series of mouse models of hypomorphic Pten has revealed the tremendous functional consequences of a subtle reduction in PTEN protein levels, which can promote cancer susceptibility and favor tumor progression. Additionally, increased PTEN levels in transgenic models result in viable mice displaying a tumor-resistant, anti-Warburg metabolic state. Thus, PTEN plays a critical dose-dependent role in tumor suppression, and therefore, understanding the regulatory mechanisms that fine-tune PTEN activity has become a paramount therapeutic goal.
PTEN function can be compromised via genetic disruption, which results in a stepwise loss of PTEN (50% or 100%). Posttranslational modifications, including ubiquitination and deubiquitination, of PTEN can fine-tune PTEN functionality via a continuum of tumor suppression. Notably the phenotypes acquired throughout the continuum of functional PTEN loss are differentially manifested depending on tissue type.

mediated PTEN regulation\(^\text{30}\); specifically, PTEN monoubiquination leads to either PTEN translocation to the nucleus or exosomal transport (by NEDD4-1)\(^\text{11,12}\), while PTEN polyubiquitination suppresses its stabilization (NEDD4-1 and WWP2)\(^\text{27,28}\) or dimerization and subsequent membrane recruitment (WWP1)\(^\text{25,26}\).

Increasing evidence has shown that deregulated deubiquitination leads to detrimental effects on PTEN levels and subcellular partitioning to promote tumorigenesis. Deubiquitinating enzymes (DUBs) are proteases that deconjugate ubiquitin from ubiquitinated substrates and thereby remodel polyubiquitin chains on target proteins to counteract the protein ubiquitination mediated by E3 ubiquitin ligases\(^\text{36}\). DUBs are categorized into two major classes, cysteine proteases and metalloproteases. The former class includes six main superfamilies\(^\text{36}\): ubiquitin-specific protease (USP), ubiquitin C-terminal hydrolase (UCH), ovarian tumor protease (OTU), Machado–Joseph disease protease, and the MDM2 homolog MDM4\(^\text{48}\). In overexpression experiments, HAUSP has been shown to bind to, deubiquitinate, and stabilize p53\(^\text{39}\), whereas disruption of HAUSP in the p53 MDM2 pathway. The C-terminal UBL domains

**Fig. 1** The PTEN continuum in tumor suppression. PTEN function can be compromised via genetic disruption, which results in a stepwise loss of PTEN (50% or 100%). Posttranslational modifications, including ubiquitination and deubiquitination, of PTEN can fine-tune PTEN functionality via a continuum of tumor suppression. Notably, the phenotypes acquired throughout the continuum of functional PTEN loss are differentially manifested depending on tissue type.

**Fig. 2** Schematic diagram of the domain architecture of DUBs. Two classes of proteases (cysteine proteases and metalloproteases) are DUBs, with most DUBs cysteine proteases. Cysteine protease DUBs can be classified into six subfamilies based on their DUB domains: USP, UCH, OTU, MJD, MINDY, and ZUFSP. Metalloprotease DUBs include a JAMM DUB domain. USP, ubiquitin-specific protease; UCH, ubiquitin C-terminal hydrolase; OTU, ovarian tumor protease; MJD, Machado–Joseph disease protease; MINDY, motif interacting with Ub-containing novel DUB family; ZUFSP, zinc finger with UFM1-specific peptidase domain; JAMM, JAB1/MPN/Mov34 metalloenzyme.

**HERPESVIRUS-ASSOCIATED UBQUITIN-SPECIFIC PROTEASE (HAUSP)/UBQUITIN-SPECIFIC PROTEASE 7 (USP7)**

HAUSP (also known as USP7) was first identified as a protein that binds herpes simplex virus E3, ubiquitin ligase ICP0, and Epstein–Barr virus nuclear antigen 1 (EBNA1)\(^\text{46}\), indicating its relevance in key cellular processes important in viral infection. All USPs share a conserved catalytic core, while their unique substrate specificity is determined by various accessory substrate-binding domains tethered to a catalytic domain\(^\text{36}\). HAUSP contains an NH2-terminal tumor necrosis factor receptor-associated factor (TRAF)-like domain, a central catalytic core, and five ubiquitin-like (UBL) domains in the COOH terminus\(^\text{37}\). The TRAF-like domain in HAUSP can recognize the P/AxxS motifs shared by all TRAF-like domain-binding substrates, including EBNA1, the tumor suppressor p53, the ubiquitin E3 ligase MDM2, mouse double minute 2, and the MDM2 homolog MDM4\(^\text{48}\). In overexpression experiments, HAUSP has been shown to bind to, deubiquitinate, and stabilize p53\(^\text{39}\); whereas disruption of HAUSP expression in human cells and transgenic mice resulted in acquisition of the opposite phenotypes, leading to stabilization and functional activation of p53 due to the destruction of MDM2\(^\text{50,51}\) which suggests a dynamic role for HAUSP in the p53–MDM2 pathway. The C-terminal UBL domains can regulate the activation and specificity of HAUSP\(^\text{52}\) and function as additional platforms for substrate binding to highly basic motifs (R/KxKxxxR) within its substrates, including ICP0, UHRF1, DNMT1 and RNF169\(^\text{53}\).

HAUSP was identified as the first bona fide PTEN deubiquitase\(^\text{41}\) (Fig. 3) and can interact with PTEN both in vitro and in vivo. The domains of HAUSP critical for binding PTEN have not been determined, but the PTEN protein contains four P/AxxS motifs and an R/KxKxxxR motif; therefore, it will be interesting to identify the domain(s) of HAUSP that bind PTEN, the true PTEN sequence identity is unknown. As ongoing research reveals the precise molecular mechanisms by which cancer-specific deubiquitination of PTEN regulates its roles in the pathobiology of cancer, the ability to pharmacologically modulate or otherwise counteract specific DUBs of PTEN, both selectively and in combination, is becoming a critical area of investigation for cancer prevention and treatment. In this review, we summarize the pathological and functional mechanisms of PTEN DUBs and describe how their functions dictate cancer cell biology and physiology while highlighting opportunities for therapeutic intervention.
to disrupt PTEN function. Indeed, HAUSP is overexpressed and associated with unfavorable prognosis in many different types of human cancers, including brain, breast, cervical, lung, prostate, skin, stomach, and hematopoietic cancers. HAUSP expression and PTEN nuclear exclusion are strongly and positively correlated in human cancers. Intriguingly, various regulatory mechanisms in cancer influence the propensity of HAUSP to mediate PTEN deubiquitination. For example, in leukemias and prostate cancer, promyelocytic leukemia (PML) plays a critical regulatory role by inhibiting HAUSP activity through death domain-associated protein (DAXX), which in turn favors PTEN nuclear localization. Similarly, nucleophosmin/B23 counteracts HAUSP-mediated deubiquitination and subsequent shuttling of PTEN to the cytoplasm, supporting the notion that PTEN is delocalized in acute myeloid leukemia with mutated nucleophosmin (e.g., NPMc+). In contrast, BCR-ABL and thyroid hormone receptor-interacting protein 13 (TRIP13) enhance deubiquitination and nuclear exclusion of PTEN through activation of HAUSP in chronic myeloid leukemia and multiple myeloma, respectively. These clinical and functional studies suggest that aberrant activation or overexpression of HAUSP may promote tumorigenesis, making HAUSP a target for therapeutic intervention in strategies to restore normal PTEN localization and tumor-suppressive function, as we discuss further below.

**UBIQUITIN-SPECIFIC PROTEASE 10 (USP10)**

USP10 is a deubiquitinase involved in diverse cellular processes, including the DNA damage response, metabolic homeostasis, and ribosome recycling. Upon DNA damage, USP10 accumulates in the nucleus, where it is phosphorylated by ATM kinase, and subsequently deubiquitinates p53. USP10 also interacts with deubiquitinates and enhances the activity of the master energy-sensor AMP-activated protein kinase-α (AMPK). Furthermore, USP10 can deubiquitinase Beclin1, a key promoter of autophagy, and protect it from degradation, thus promoting autophagy. Interestingly, Beclin1 also controls the protein stability of USP10 by regulating its deubiquitinating activity, forming a feedback loop. Similarly, USP10 prevents lysosomal degradation of 40 S subunits of ribosomes and ensures ribosome recycling associated with autophagy. Given the importance of the energy balance and autophagy in metabolic disease, USP10 may represent a potential drug target for metabolic syndrome. Furthermore, the role of USP10 in cancer has recently been expanded to include deubiquitinase activity for PTEN. Indeed, USP10 restores the membrane localization and phosphatase activity of PTEN by reversing the tripartite motif-containing 25 (TRIM25)-mediated K63-linked polyubiquitination found in lung cancer. Since USP10 is frequently downregulated in human cancers, including lung, gastric, colorectal, and small intestinal carcinomas, restoration of USP10 function may represent a new therapeutic strategy for cancer prevention and treatment through PTEN reactivation.

**UBIQUITIN-SPECIFIC PROTEASE 11 (USP11)**

USP11 was originally identified as one of inherited X-linked retinal disorder genes at Xp11.23, although a common deletion within the USP11 interval has been also found in ovarian cancer. X-linked tumor suppressor genes are potentially significant to

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**Fig. 3 Proposed model showing the mechanisms of DUB action for PTEN.** While HAUSP/USP7 induces deubiquitination and subsequent nuclear exclusion of monoubiquitinated PTEN in the nucleus, where it can control the cell cycle and genomic stability, PML-RARα, NPMc+, and BCR-ABL promote HAUSP-mediated PTEN deubiquitination in blood-borne cancers. USP11 plays a role in the maintenance of the effective levels of both nuclear and cytosolic PTEN for tumor suppression, and interestingly, its expression and activity are regulated by the PTEN/Pi3K pathway. Furthermore, in the cytoplasm, USP11, USP13, and (acetylated) OTUD3 catalyze the removal of the K48-linked polyubiquitin chain on PTEN to enhance protein stability, whereas USP10 recognizes and removes the K63-linked polyubiquitin chain from PTEN, leading to PTEN recruitment to the plasma membrane. Ataxin-3 represses PTEN by inhibiting its transcription. PTEN phosphatase and tensin homolog deleted on chromosome 10, HAUSP herpesvirus-associated ubiquitin-specific protease, USP10 ubiquitin-specific protease 10, USP11 ubiquitin-specific protease 11, USP13 ubiquitin-specific protease 13, OTUD3 OTU deubiquitinase 3, PI3K phosphoinositide 3-kinase, PIP2 phosphoinositide-4,5-biphosphate, PIP3 phosphoinositide-3,4,5-triphosphate, mTOR mammalian target of rapamycin, PML promyelocytic leukemia, NPMc+ cytoplasmic nucleophosmin, TRIP13 thyroid hormone receptor-interacting protein 13.
tumorigenesis because they can be functionally silenced by loss of heterozygosity or mutation of a single allele. A recent and extensive review described USP11 as a predictive and prognostic factor in human cancers of various histologies. Indeed, USP11 is often repressed in brain, breast, skin, and prostate cancers but upregulated in colorectal and hepatocellular carcinomas. As a deubiquitinase, USP11 interacts with multiple substrate proteins linked to cancer-related pathways. For example, USP11 recruits BRCA1 to chromatin by deubiquitinating PALB2 (partner and localizer of BRCA2) in a cell cycle-dependent manner or stabilizing MYCN in neuroblastoma. Notably, USP11 has been found to be rapidly lost after DNA damage in a manner dependent on ATM/ATR induction. In brain tumors, USP11 deubiquinates and stabilizes PML, and its transcription is dependent on ATM/ATR induction. In brain tumors, USP11 is localized adjacent to USP13, which is frequently amplified in human cancers such as brain, lung, ovarian, esophageal and cervical cancers, and high USP13 expression is correlated with poor survival outcomes. Furthermore, OTUD3 has been identified as a potential deubiquitinase for PTEN and, in contrast, maintains the stability of the oncoprotein PTEN and thus a tumor suppressor in breast cancer (Fig. 3). OTUD3 may require its acetylation, it will be interesting to determine whether OTUD3 acetylation is also involved in PTEN regulation. Nevertheless, an intriguing puzzle has been suggested that aberrant OTUD3 expression may be associated with obesity and a high risk of diabetes. Emerging evidence has suggested cancer-associated functions of OTUD3 in multiple types of human cancer. For example, OTUD3 interacts with the ZFP36 ring finger protein through its OTU region and stabilizes it by inhibiting FBXW7-mediated ubiquitination, which in turn induces VEGF-C mRNA decay to prevent lymphatic metastasis of human esophageal cancer. Furthermore, OTUD3 has been identified as a potent deubiquitinase for PTEN and thus a tumor suppressor in breast cancer (Fig. 3). OTUD3 (OTU region) directly interacts with PTEN (C2 domain), deubiquitinating and stabilizing the PTEN protein to suppress PI3K-AKT signaling. OTUD3 transgenic mice exhibit higher PTEN expression and show a reduced tendency for breast cancer tumorigenesis. The reduction in OTUD3 expression, concomitant with decreased PTEN protein levels, correlates with breast cancer aggressiveness and poor prognosis. As the full activation of OTUD3 may require its acetylation, it will be interesting to determine whether OTUD3 acetylation is also involved in PTEN regulation. Nevertheless, an intriguing puzzle has been suggested following a recent study of the accelerated development of lung carcinomas after deletion of Otud3 in mice. In contrast to its level in breast cancer, OTUD3 is highly expressed in human lung cancer, and its upregulation is associated with unfavorable prognoses. Furthermore, in lung cancer, OTUD3 fails to regulate PTEN and, in contrast, maintains the stability of the oncoprotein GRP78 (glucose-regulated protein 78-kDa), showing the tumor tissue complexity of the functional role of played by a given deubiquitinase. These findings suggest that future studies should optimize the accurate stratification of deubiquitinase-targeted therapies for specific organs or tissues.
**ATAXIN-3 (ATXN3)**
Machado-Joseph disease (MJD, also known as spinocerebellar ataxia type 3 or SCA3) is the most common dominant ataxia in the world and is caused by abnormal expansion of CAG repeats in a coding region of ATXN3, which produces an elongated polyglutamine (polyQ) tract in the Ataxin-3 protein. Ataxin-3 contains an NH2-terminal ubiquitin-protease (Josephin) domain and COOH-terminal polyQ stretch and ubiquitin-interacting motifs. As a deubiquitinase, Ataxin-3 plays a role in protein stability, suggesting that its role is independent of direct PTEN deubiquitination.

**TARGETING PTEN DUBS FOR CANCER THERAPY**
PTEN is a bona fide lipid phosphatase that opposes the activation of the highly oncogenic PI3K-AKT-mTOR pathway and is considered a major dose-dependent tumor suppressor. While PTEN itself is not considered a ‘druggable’ target, the pathological mechanisms that modulate PTEN protein levels and activity offer possible routes for cancer therapy. Furthermore, the predominant genetic change associated with loss of function is deletion of only one single gene copy of PTEN, underscoring the importance of targeting the nongenomic mechanisms of PTEN loss of function for the prevention and treatment of cancer. Along with the previously mentioned biological and clinical relevance of PTEN DUBs in tumorigenesis, PTEN DUBs may represent promising targets for therapeutic PTEN reactivation regimens in many types of cancer. Therefore, the activity of PTEN DUBs can likely be pharmacologically manipulated to fully reactivate PTEN, resulting in new and innovative approaches to the prevention and treatment of cancer (Table 1). Indeed, a small-molecule inhibitor of HAUSP/USP7, PS091, has been shown to restore the monoubiquitination and nuclear localization of endogenous PTEN and to induce cell growth arrest and apoptosis in blood-born cancers. In addition to PTEN, p53 is upregulated by PS091, but its cytotoxic activity is not dependent on p53. Other recently developed (pre)clinical HAUSP inhibitors (e.g., FT671, XL188, and GNE6640) will need to be used to establish a portfolio of HAUSP-PTEN axis-targeting drugs for use in future cancer therapies. Additionally, successful PTEN reactivation through disruption of the PML-DAXX-HAUSP complex by Trisenox (arsenic trioxide), which is currently used to treat patients with acute promyelocytic leukemia, may pave the way to clinical trials for prevention and therapy for solid tumors at large.

**CONCLUDING REMARKS**
PTEN antagonizes the oncogenic PI3K-AKT-mTOR signaling pathway, which is frequently activated in cancers. PTEN deletions are often found in more aggressive tumors and are associated with worsened prognosis, increased tumor metastases, and a greater chance of recurrence after treatment. Emerging evidence has also shown that, similar to the genomic disruptions that inactivate a given PTEN allele, ‘nongenomic’ pathological mechanisms that reduce PTEN protein levels and activity are associated with cancer. As a result, identifying active deubiquitinating enzymes that directly modulate PTEN protein stability and activity for therapeutic purposes has become a high priority for cancer researchers. Indeed, new discoveries of DUBs that interact with PTEN have changed our understanding of PTEN function and regulation. HAUSP/USP7, USP10, USP11, USP13, OTUD3, and Ataxin-3 have all been recently identified as PTEN DUBs that control PTEN activity in different cancer-specific contexts. However, these DUBs play context-dependent tumor suppressor or oncogenic roles in cancer progression, and in different contexts,

| DUBs | Compounds | Effects on DUBs | Effects on PTEN | References |
|------|-----------|----------------|----------------|------------|
| USP7 | PS091 | Inhibition | Nuclear localization | 58,66 |
|      | FT671, FT827 | Inhibition | ND | 109 |
|      | XL188 | Inhibition | ND | 110 |
|      | GNE6640, GNE6776 | Inhibition | ND | 111 |
|      | Compound 2, 4, 5 | Inhibition | ND | 120 |
|      | HBX-19818, HBX-28258 | Inhibition | ND | 121 |
| USP10 | Spautin-1 | Inhibition | ND | 70 |
|      | Metformin | Activation | ND | 112 |
| USP11 | Mitoxantrone | Inhibition | ND | 122 |
|      | Resveratrol | Activation | Stability | 43 |
|      | Psammaplysene A | Activation | Stability | 43 |
| USP13 | Spautin-1 | Inhibition | ND | 70 |
| OTUD3 | Rolapitant | Inhibition | ND | 123 |
|      | Ex-527 | Activation | ND | 124 |
| Ataxin-3 | Eeyarestatin-1 | Inhibition | ND | 125 |
both their up- and downregulation can be hallmarks of tumor cells leading to malignancies; therefore, a complete understanding of how each individual DUB functionally influences tumorigenesis or tumor suppression remains unclear, and further in vivo investigation is required. Although researchers have extensively described the specificity of PTEN DUBs, as discussed herein, their ubiquitin linkage specificity (i.e., K6, K11, K27, K29, K33, K48 or K63-linked mono- and polyubiquitin chains) with respect to PTEN is still being elucidated. In addition, whether and how the complex relationship between PTEN DUBs (e.g., HAUSBUPT111, HAUBUSP111,15 and USP10–USP13113) strengthens their activity toward PTEN requires further study. It will be interesting to evaluate the possible crosstalk between deubiquitination and other posttranslational modifications, such as acetylation115,116, methylation,117 and SUMOylation117 during the control of PTEN stability and activity. Given recent discoveries revealing that distinct PTEN isoforms and active PTEN dimers are related to specific PTEN functions, it will be interesting to determine whether and how the aforementioned and several other PTEN DUBs117–119 impact the stability, localization and biological activity of dimeric PTEN and various PTEN isoforms. PTEN is a major tumor suppressor protein whose expression and activity often serve as the bases of diagnostic and prognostic assessment; however, no available therapy that directly targets PTEN itself is currently available. With the link of DUBs to reactivated PTEN established, the pharmacological manipulation of DUBs holds great clinical promise and suggests innovative and effective therapeutic approaches.

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**AUTHOR CONTRIBUTIONS**

The research was conceived and designed by A.C., M.K.P., S.J.S., and M.S.S. The manuscript was written by A.C., M.K.P., S.J.S. and M.S.S.

**COMPETING INTERESTS**

The authors declare no competing interests.

**ADDITIONAL INFORMATION**

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