

EXTENDED METHODS

Immunofluorescence (IF) assays

Cells cultured on glass cover slips were fixed with 4% formaldehyde in PBS for 15 minutes at room temperature. The cells were permeabilized with 0.1% Triton X-100 in PBS for 5 minutes on ice. After washing 3 times in PBS, the samples were blocked for 30 minutes with 5% control goat serum. The samples were incubated with primary antibodies for 2 h at room temperature. After rinsed 3 times using PBST containing 0.1% Tween-20, the coverslips incubated with Alexa-594-conjugated goat anti-mouse secondary antibody (Invitrogen) for 1 h and washed 3 times with PBST, the nucleus was stained with 4, 6-diamidino-2-phenylindole (DAPI) for 10 minutes. Coverslips were rinsed 2 times with PBS and mounted onto slides.

Dot immunoblot assays

Peptides were spotted onto nitrocellulose membrane allowing solution to penetrate membrane (usually 3-4 mm diameter) by applying it slowly in 1 μ l increments. The membrane was dried, and blocked in TBST buffer with 5% non-fat milk for immunoblot analysis with indicated antibodies.

Laser micro-irradiation and IF assays

HCT116-*PTEN*^{-/-} cells stably expression of HA-PTEN were cultured for 48 hr prior to irradiation with 10 μ M BrdU4 (Sigma-Aldrich, Cat # B9285). UVA laser (50 mW) irradiation was conducted using an inverted microscope (Eclipse Ti; Nikon) with a Palm microbeam laser microdissection workstation. Following irradiation, cells were incubated at 37 °C for 5 minutes, washed once with cold PBS, and then fixed with PBS containing 4% paraformaldehyde (PFA) for 10 min at room temperature. Cells were then washed three times with cold PBS and permeabilized with PBS containing 0.5% Triton-X100 for 30 min. After permeabilization, cells were washed with IF blocking buffer (PBS containing 1% BSA, 10% FBS, 0.25% Triton-X100, 0.02% NaN₃), and then co-stained using antibodies for HA and γ H2ax at 4°C overnight. Staining was conducted with fluorescent secondary and DAPI.

Colony formation assays

Cells were seeded in 6-well plates (3000 cells/well) and pre-treated with/without 1 μM BKM120 or 2 μM DZNep for 24 h followed by additional IR (0.5 Gy) or etoposide treatment as indicated for 24 hours. Cells were incubated for 6-10 days until formation of visible colonies. Colonies were fixed with 10% acetic acid/10% methanol for 20 min and stained with 0.4% crystal violet/20% ethanol for 20 min. After staining, the plates were washed with distilled water and air-dried. The colony number was counted.

Figure S1

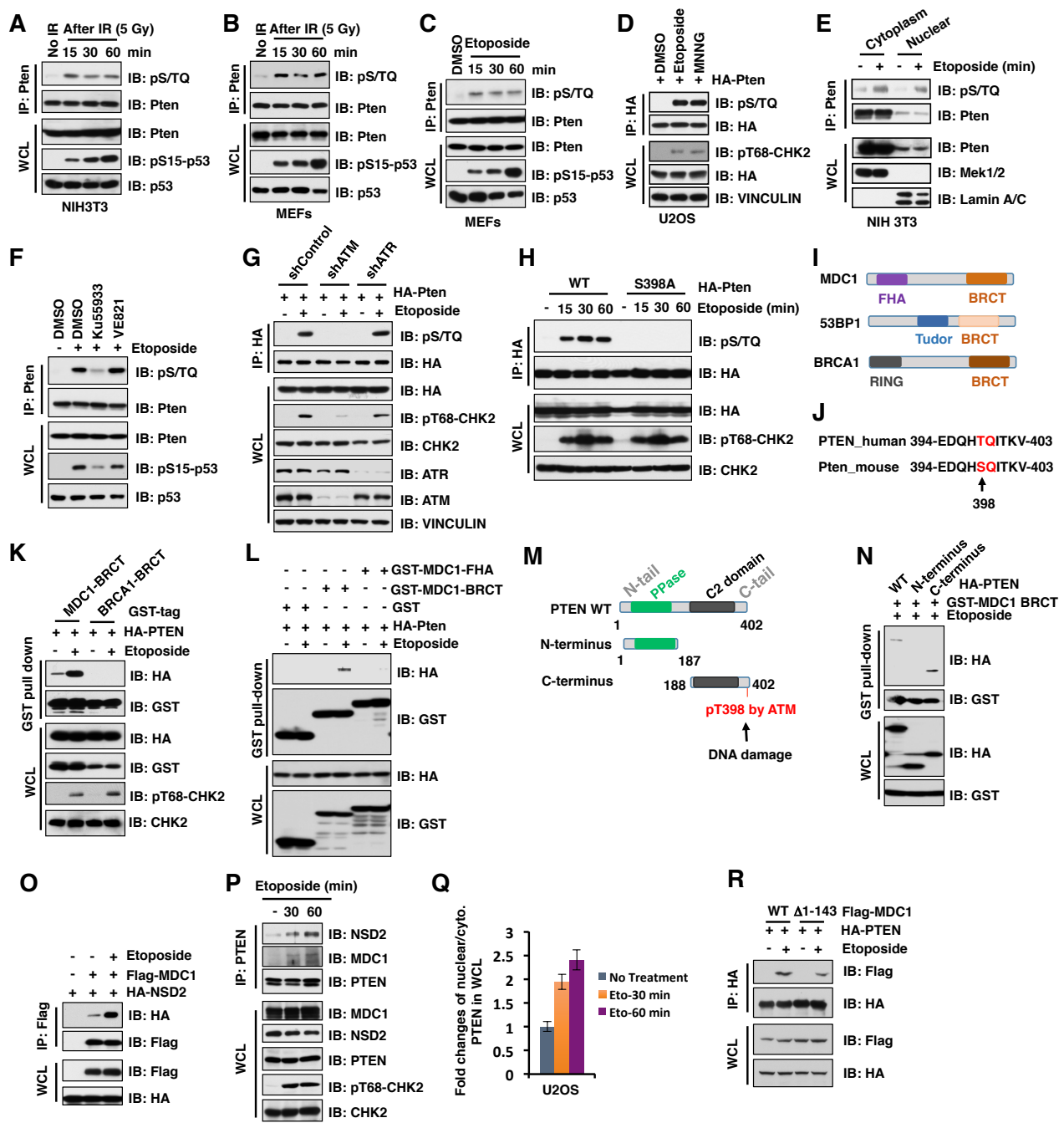


Figure S1. DNA-damaging agents induce PTEN, MDC1 and NSD2 to form a tertiary complex, which is required for ATM-mediated phosphorylation of PTEN.

- (A and B) Pten was detected using the phospho-(Ser/Thr) ATM/ATR substrate antibody (pS/TQ) upon irradiation (IR) treatment. Immunoblot (IB) analysis of anti-Pten immunoprecipitations (IPs) and whole cell lysates (WCL) derived from NIH3T3 (A) or MEFs (B) after irradiation (IR, 5 Gy) treatment at indicated time points before harvesting.
- (C and D) PTEN was detected using the phospho-(Ser/Thr) ATM/ATR substrate antibody (pS/TQ) upon etoposide or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) treatment. IB analysis of anti-Pten or anti-HA IPs and WCL derived from MEFs or U2OS cells after treatment with/without 30 μ M etoposide at indicated time points (C) or MNNG (500 μ M) for 30 min (D) before harvesting.
- (E) Etoposide-induced phosphorylation of Pten existed in both cytoplasm and nucleus. IB analysis of anti-Pten IPs from cytoplasm or nucleus as well as WCL derived from NIH3T3 cells treatment with 30 μ M etoposide as indicated time points before harvesting.
- (F) ATM inhibitor, but not ATR inhibitor, inhibited etoposide-induced phosphorylation of Pten. IB analysis of anti-Pten IPs and WCL derived from NIH3T3 cells pre-treated with 1 μ M Ku55933 (ATM inhibitor) or 1 μ M VE821 (ATR inhibitor) for 90 minutes (min) followed by addition of 30 μ M etoposide for 30 min before harvesting.
- (G) Depletion of *ATM*, but not *ATR*, impaired etoposide-induced phosphorylation of PTEN. IB analysis of anti-HA IPs and WCL derived from U2OS cell lines stably expressing shControl or shATM transfected with indicated constructs. 36 h after transfection, cells were treated with/without 30 μ M etoposide for 30 min before harvesting.
- (H) Etoposide treatment induced the phosphorylation of Pten wild type (WT), but not the S398A mutant. IB analysis of anti-HA IPs and WCL derived from 293T cells that ectopically expressing HA-tagged WT or S398A mutant mouse Pten. 36 h after transfection, 30 μ M etoposide was added and cells were harvested at indicated time points for IP analysis.
- (I) A schematic representation of the indicated domains of 53BP1, MDC1 and BRCA1.
- (J) Sequence alignment of PTEN C-tails between human and mouse.
- (K and L) Etoposide treatment enhanced PTEN interaction with MDC1 BRCT domain. IB analysis of GST pull-down precipitations and WCL derived from U2OS cells treated with/without 30 μ M etoposide for 30 min before harvesting.

- (M)** A schematic representation of the indicated domains of PTEN, including N-terminus (N-tail and phosphatase domain) and C-terminus (C2 and C-tail domain).
- (N)** MDC1 BRCT domain interacted with the C-terminal domain of PTEN. IB analysis of GST pull-down precipitations and WCL derived from U2OS cells treated with 30 μ M etoposide for 30 min before harvesting.
- (O)** Etoposide treatment enhanced MDC1 interaction with PTEN. IB analysis of anti-Flag IPs and WCL derived from U2OS transfected with indicated constructs. 36 h after transfection, cells were treated with/without 30 μ M etoposide for 30 min before harvesting.
- (P)** PTEN, MDC1, and NSD2 formed a tertiary complex upon etoposide treatment. IB analysis of anti-PTEN IPs and WCL derived from U2OS cells treated with 30 μ M etoposide as indicated time points before harvesting.
- (Q)** The ratio of cytoplasmic/nuclear PTEN quantification in WCL of Fig. 1D. PTEN bands intensity was quantified using the ImageJ software.
- (R)** Etoposide treatment promoted PTEN interaction with MDC1 in cells. IB analysis of anti-HA IPs and WCL derived from 293T cells treated with 30 μ M etoposide for 30 min before harvesting.

Figure S2

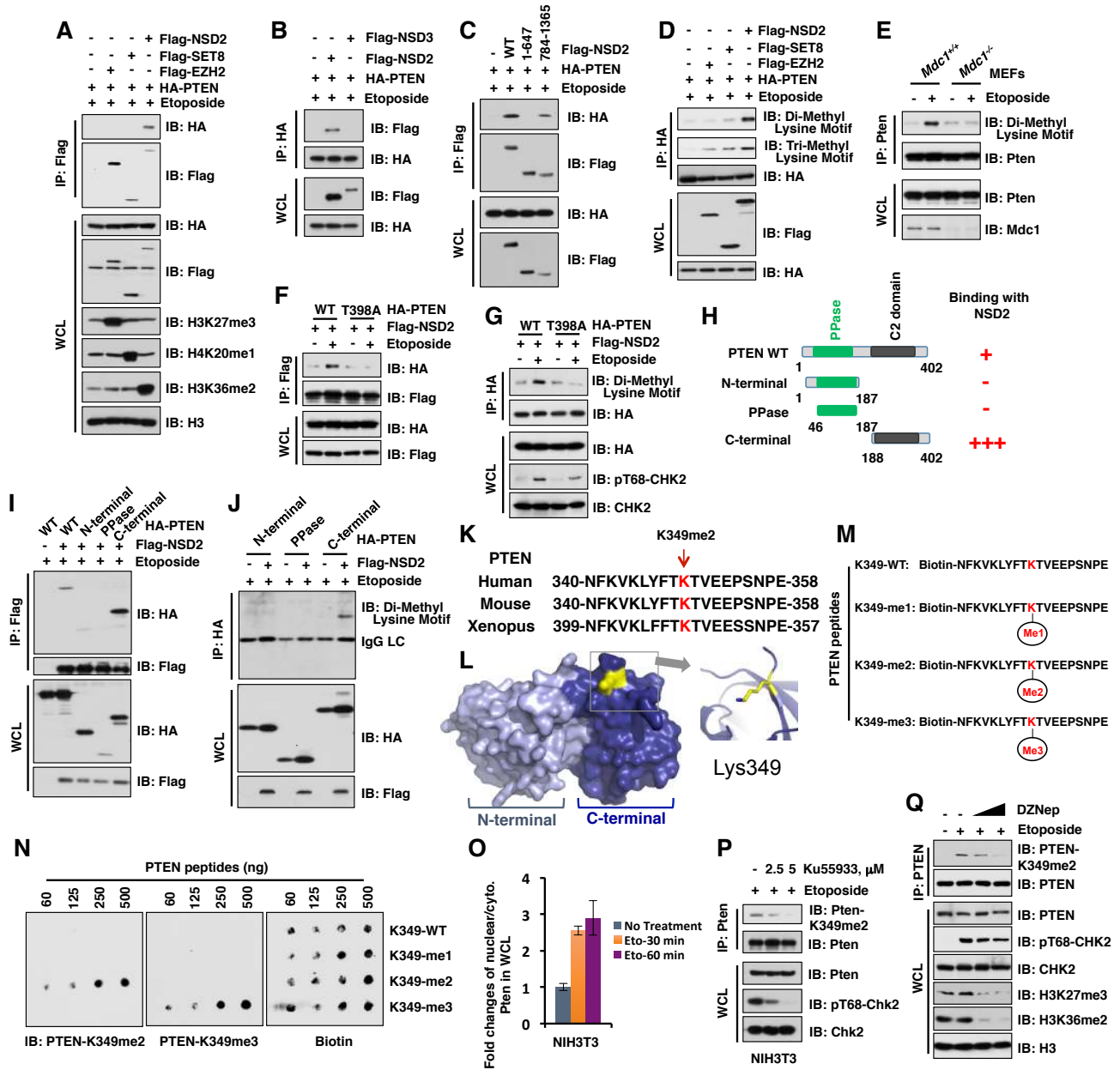


Figure S2. The NSD2 methyltransferase specifically interacts with PTEN and promotes the methylation of PTEN at K349.

- (A and B)** NSD2, but not SET8, EZH2 nor NSD3 methyltransferases, specifically interacted with PTEN. IB analysis of anti-Flag **(A)** or anti-HA **(B)** IP and WCL derived from HEK293T or HEK293 cells transfected with indicated constructs and treated with 30 μ M etoposide for 30 min before harvesting.
- (C)** NSD2 interacted with PTEN largely through its C-terminal domain (784-1365). IB analysis of anti-Flag IP and WCL derived from HEK293 cells transfected with indicated constructs and treated with 30 μ M etoposide for 30 min before harvesting.
- (D)** NSD2, but not SET8 and EZH2, promoted methylation of PTEN. IB analysis of anti-HA IPs and WCL derived from HEK293T cells transfected with indicated constructs and treated with 30 μ M etoposide for 30 min before harvesting.
- (E)** *Mdc1* deficiency impaired the di-methylation of Pten upon etoposide treatment. IB analysis of anti-Pten IPs and WCL derived from *Mdc1*^{+/+} and *Mdc1*^{-/-} MEFs treated with 30 μ M etoposide for 30 min before harvesting.
- (F)** Etoposide treatment enhanced PTEN WT, but not T398A mutant, interacting with NSD2. IB analysis of anti-Flag IPs and WCL derived from U2OS cells co-transfected with HA-PTEN WT or T398A mutant with Flag-NSD2 and treated with/without etoposide for 60 min before harvesting.
- (G)** Etoposide treatment promoted the di-methylation of WT, but not T398A mutant. IB analysis of anti-HA IPs and WCL derived from U2OS cells co-transfected with indicated constructs and treated with/without 30 μ M etoposide for 60 min before harvesting.
- (H)** A schematic representation of the indicated domains of PTEN, including N-terminus (N-tail and phosphatase domain) and C-terminus (C2 and C-tail domain), which is required for PTEN interaction with NSD2.
- (I)** NSD2 interacted with PTEN largely through the C-terminal domain of PTEN upon etoposide treatment. IB analysis of anti-Flag IPs and WCL derived from HEK293T cells transfected with the indicated constructs and treated with 30 μ M etoposide for 30 min before harvesting.
- (J)** Di-methylation occurred on the C-terminal domain of PTEN. IB analysis of anti-HA IPs and WCL derived from HEK293T cells transfected with the indicated constructs and treated with/without 30 μ M etoposide for 30 min before harvesting.
- (K)** The sequence alignment of PTEN among different species to illustrate that the K349 di-methylation

site (K349me₂) is evolutionarily conserved.

- (L) A surface diagram of the crystal structure of PTEN (PDB code: 1D5R). The N-terminal domain of PTEN is in light blue, and C-terminal domain is in dark blue. The identified Lys349, colored by yellow, is located at the outer face of PTEN C-terminal domain. The structure model was analyzed using the PyMOL software.
- (M) A schematic representation of the various biotinylated synthetic PTEN-derived peptides covering aa 340-358 of PTEN.
- (N) Validation of antibodies that specifically recognized K349 di-methylation (K349me₂) of PTEN. Each indicated synthetic peptide in (M) was diluted and used for the dot immunoblot analysis with the anti-PTEN-K349me₂, anti-PTEN-K349me₃ or anti-Biotin antibody, respectively.
- (O) The ratio of cytoplasmic/nuclear Pten quantification in WCL of Fig. 2E. Pten bands intensity was quantified using the ImageJ software.
- (P) ATM inhibitor (Ku55933) inhibited di-methylation of Pten. IB analysis of anti-Pten IPs and WCL derived from NIH3T3 cells treated with 2.5 μM or 5 μM Ku55933 for 24 hours followed by addition of 30 μM etoposide for 30 min before harvesting.
- (Q) DZNep (a pan-inhibitor of *S*-adenosylmethionine-dependent methyltransferase) inhibited di-methylation of PTEN. IB analysis of anti-PTEN IPs and WCL derived from U2OS cells treated with 2 μM or 5 μM DZNep for 48 hours followed by addition of 30 μM etoposide for 30 min before harvesting.

Figure S3

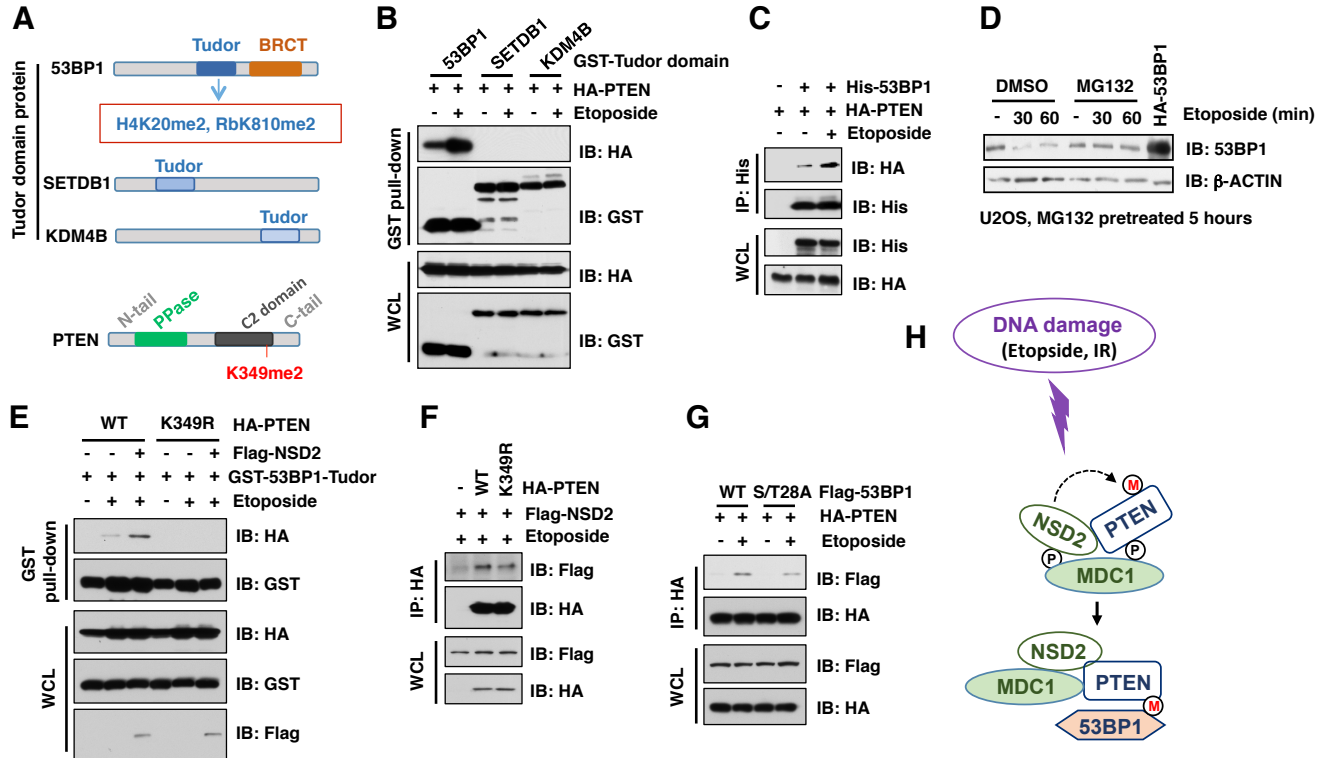


Figure S3. 53BP1 recognizes the K349 di-methylation species of PTEN largely through its tudor domain.

- (A) A schematic illustration of the indicated tudor domains derived from 53BP1, SETDB1 or KDM4B.
- (B) Etoposide treatment promoted PTEN interaction with the tudor domain derived from 53BP1, but not SETDB1 nor KDM4B. IB analysis of GST pull-down and WCL derived from U2OS cells co-transfected with HA-PTEN with GST-tagged tudor domain derived from 53BP1, SETDB1 and KDM4. After 36 hours post transfection, cells were treated with 30 μ M etoposide for 30 min before harvesting.
- (C) Etoposide treatment enhanced PTEN interaction with 53BP1. IB analysis of anti-His IPs and WCL derived from U2OS cells treatment with/without 30 μ M etoposide for 60 min before harvesting.
- (D) IB analysis of WCL derived from U2OS cells co-transfected with indicated constructs. Cells were pretreated with MG132 for 5 hours before exposing to etoposide for indicated time points.
- (E) Etoposide treatment promoted PTEN WT, but not K349R interaction with the tudor domain of 53BP1. IB analysis of GST pull-down and WCL derived from HEK293 cells co-transfected with indicated constructs. After 36 hours post transfection, cells were treated with 30 μ M etoposide for 30 min before harvesting.
- (F) PTEN-K349R still interacted with the methyltransferase NSD2 under etoposide treatment. IB analysis of anti-HA IPs and WCL derived from 293 cells co-transfected with indicated constructs. After 36 hours post transfection, cells were treated with 30 μ M etoposide for 30 min before harvesting.
- (G) 53BP1-S/T28A still interacted with PTEN under etoposide treatment. IB analysis of anti-HA IPs and WCL derived from HEK293 cells co-transfected with indicated constructs. After 36 hours post transfection, cells were treated with 30 μ M etoposide for 30 min before harvesting.
- (H) A schematic model to illustrate that DNA damage induces the interaction between the MDC1-BRCT domain and PTEN or NSD2, respectively, through a phosphorylation-dependent manner. Subsequently, NSD2 promotes the K349 di-methylation of PTEN, which is recognized by the 53BP1 tudor domain.

Figure S4

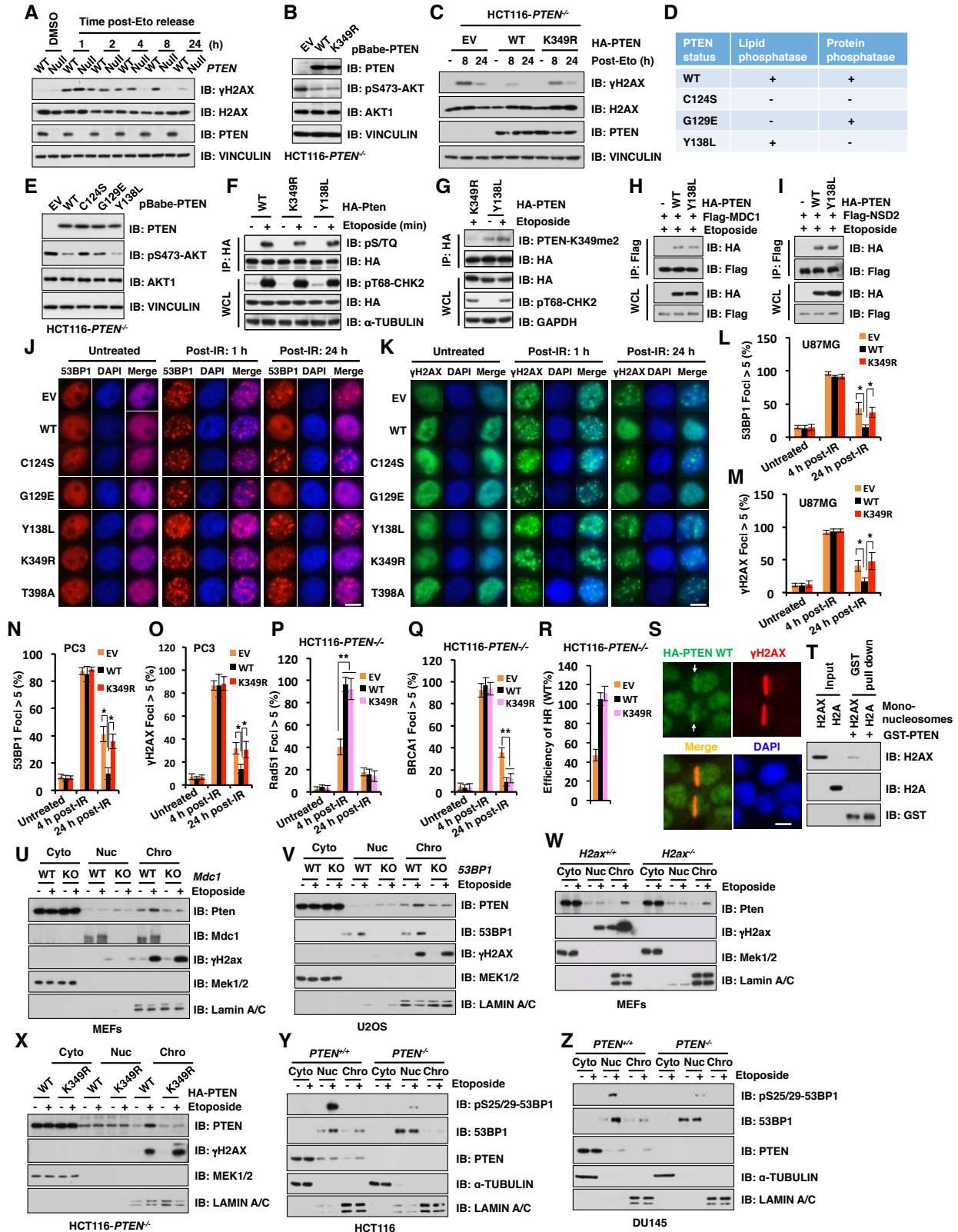


Figure S4. The protein phosphatase activity and K349 di-methylation of PTEN are required for DSBs repair process.

- (A) *PTEN* deficiency elevated γ H2AX after 4 h post-etoposide treatment. IB analysis of WCL derived from *PTEN*^{+/+} and *PTEN*^{-/-} HCT116 cells with 30 μ M etoposide treatment for 30 min and releasing cells in normal culture condition as indicated time points.
- (B) PTEN K349R mutant did not affect its lipid phosphatase activity. IB analysis of WCL derived from HCT116 *PTEN*^{-/-} cells reconstituted with the PTEN WT, K349R mutant, as well as empty vector (EV) using indicated antibodies.
- (C) PTEN-WT, but not the PTEN-K349R mutant, rescued *PTEN* deficiency mediated high levels of γ H2AX after 4 h post-etoposide treatment. IB analysis of WCL derived from *PTEN*^{-/-} HCT116 cells introducing PTEN WT, K349R as well as EV, which were treated with 30 μ M etoposide for 30 min and releasing cells in normal culture condition as indicated time points.
- (D) A table summary of the lipid versus protein phosphatase activity of reported PTEN WT and various well-characterized PTEN mutants.
- (E) IB analysis of WCL derived from HCT116 *PTEN*^{-/-} cells reconstituted with the indicated PTEN WT and PTEN-mutant proteins.
- (F) The Pten-K349R and Y138L mutants could be phosphorylated after etoposide treatment. IB analysis of anti-HA IPs and WCL derived from U2OS cells transfected with the indicated constructs and where indicated treatment with 30 μ M etoposide for 30 min before harvesting.
- (G) The PTEN-Y138L mutant could be di-methylated after etoposide treatment. IB analysis of anti-HA IPs and WCL derived from U2OS cells transfected with the indicated constructs and where indicated treatment with 30 μ M etoposide for 30 min before harvesting.
- (H and I) The PTEN-Y138L mutant still interacted with MDC1 (H) or NSD2 (I) after etoposide treatment. IB analysis of anti-Flag IPs and WCL derived from U2OS cells transfected with the indicated constructs and treated with 30 μ M etoposide for 30 min before harvesting.
- (J and K) *PTEN*^{-/-}-HCT116 cells reconstituted with indicated constructs were subjected to immunofluorescence assays with indicated antibodies as described in Methods. Representative immunofluorescence images of 53BP1 (J) or γ H2AX (K) foci were shown. Scale bar: 10 μ m
- (L and M) U87MG cells reconstituted with the indicated PTEN constructs were treated with IR (5 Gy) and immunostained at the indicated times with anti-53BP1 or anti- γ H2AX. Quantification of 53BP1

- (L) or γ H2AX (M) foci positive cells (foci > 5 per cell) was performed by counting a total of 100 cells per sample, respectively. Data are represented as mean \pm s.d., n = 3, and * p < 0.05 (Student's t -test).
- (N and O) PC3 cells reconstituted with the indicated PTEN constructs were treated with IR (5 Gy) and immunostained at the indicated times with anti-53BP1 or anti- γ H2AX. Quantification of 53BP1 (N) or γ H2AX (O) foci positive cells (foci > 5 per cell) was performed by counting a total of 100 cells per sample, respectively. Data are represented as mean \pm s.d., n = 3, and * p < 0.05 (Student's t -test).
- (P and Q) $PTEN^{-/-}$ HCT116 cells reconstituted with the indicated PTEN constructs were treated with IR (5 Gy) and immune-stained at the indicated times with anti-RAD51 or anti-BRCA1 antibody. Quantification of RAD51 (P) or BRCA1 (Q) foci positive cells (foci > 5 per cell) was performed by counting a total of 100 cells per sample, respectively. Data are represented as mean \pm s.d., n = 3, and ** p < 0.01 (Student's t -test).
- (R) PTEN-K349R mutant did not affect the efficiency of homologous recombination (HR). U87MG cells stably expressing a DR-GFP reporter were reconstituted with the PTEN-WT and K349R as well as EV, and their HR-mediated repair efficiency was measured.
- (S) HA-PTEN accumulates at sites of laser microirradiation in HCT116 cells. Scale bar: 10 μ m
- (T) The purified recombinant GST-PTEN interacted with H2AX, but not H2A containing nucleosome core particles in *in vitro*.
- (U-W) PTEN was recruited into DNA damage sites might be largely dependent on MDC1 and 53BP1, but not γ H2AX upon etoposide treatment. IB analysis of cellular fractionation samples derived from *Mdc1* KO MEFs (U), *53BP1* KO U2OS cells (V) or *H2ax*^{-/-} MEFs (W), as well as their counterpart WT cells with/without 30 μ M etoposide treatment for 30 min before harvesting.
- (X) PTEN-K349R could not be recruited into DNA damage sites upon etoposide treatment. IB analysis of cellular fractionation samples derived from $PTEN^{-/-}$ HCT116 cells reconstituted with the indicated PTEN constructs with/without 30 μ M etoposide treatment for 30 min before harvesting.
- (Y and Z) The phosphorylation of 53BP1 at S25/29 was dramatically decreased in $PTEN^{-/-}$ cells upon etoposide treatment. IB analysis of cellular fractionation samples derived from HCT116 $PTEN^{-/-}$ cells (Y) or DU145 $PTEN^{-/-}$ cells (Z), as well as their counterpart WT cells with/without 30 μ M etoposide treatment for 30 min before harvesting.

Figure S5

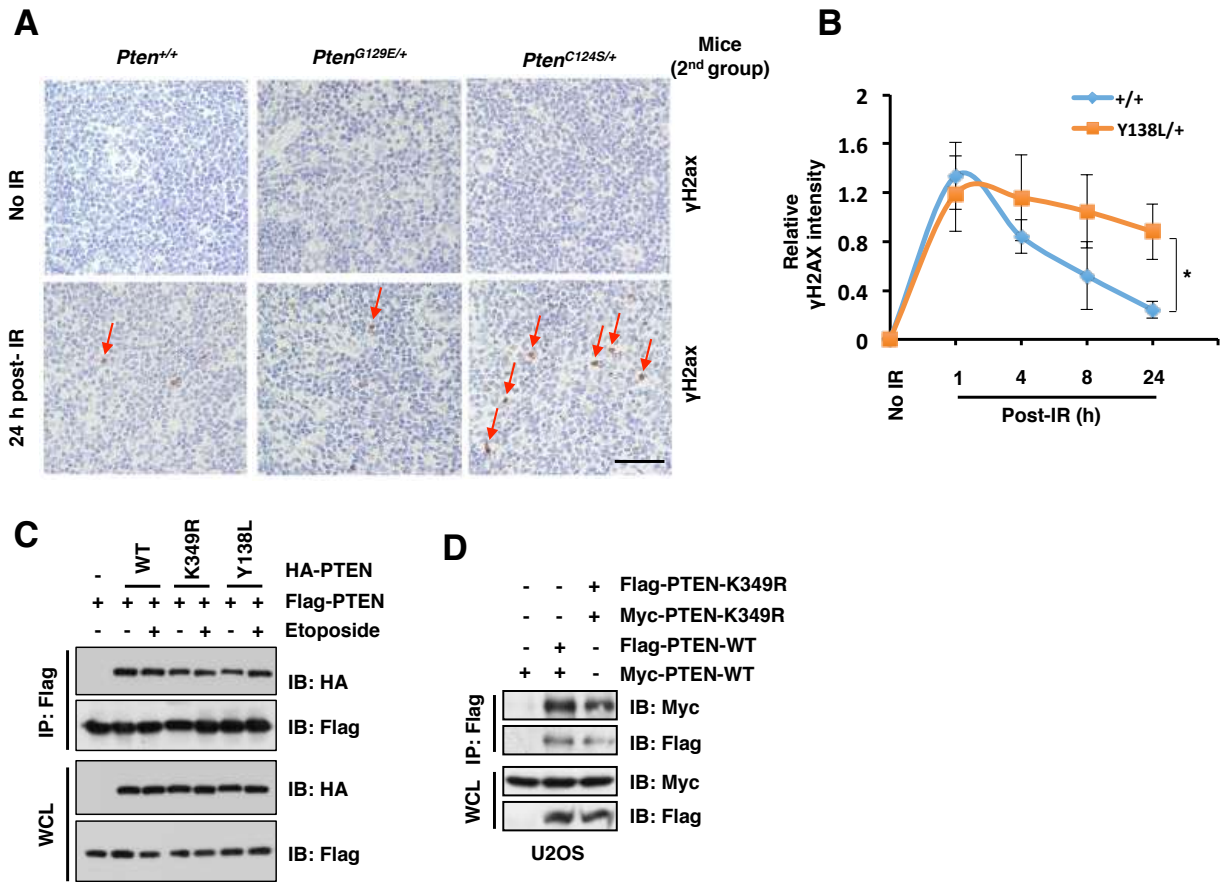


Figure S5. The protein phosphatase activity of PTEN is required for γ H2AX foci resolving *in vivo*.

- (A) Representative immunohistochemistry (IHC) analysis of spleen tissues derived from *Pten*^{+/+}, *Pten*^{G129E/+} and *Pten*^{C124S/+} mice (2nd group), which were treated with IR (3 Gy) and sacrificed at 24 h after irradiation. Scale bar, 50 μ m.
- (B) Quantification of protein intensity in **Figure 5E** was performed using the ImageJ software. γ H2AX immunoblot bands were normalized to Vinculin, and then normalized to the control (no IR treatment).
- (C and D) PTEN-K349R or Y138L mutant did not affect their dimerization. IB analysis of anti-Flag IPs and WCL derived from U2OS cells transfected with the indicated constructs and where indicated treatment with 30 μ M etoposide for 30 min before harvesting.

Figure S6

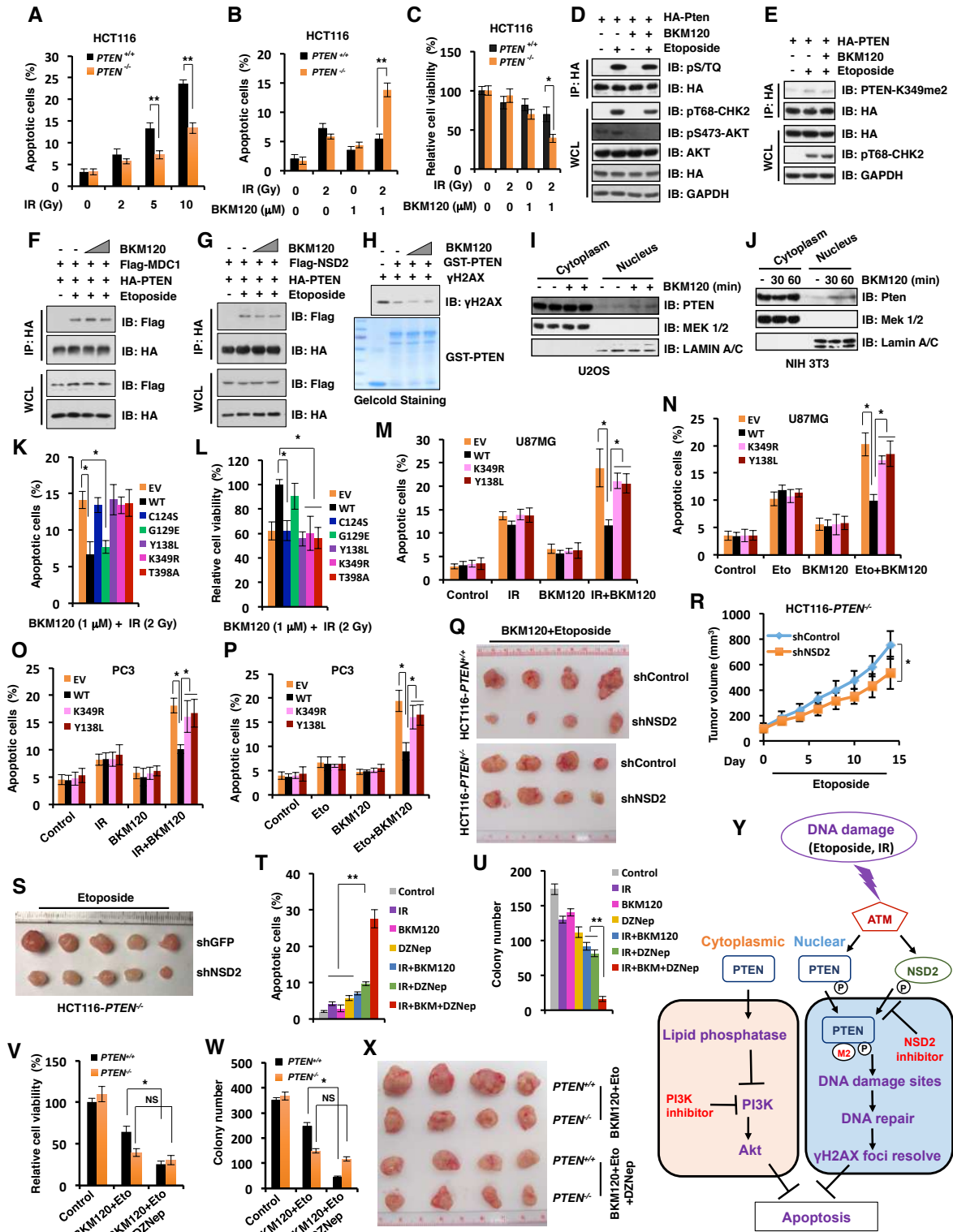


Figure S6. Loss of PTEN protein phosphatase activity or K349 methylation event sensitizes cancer cells to IR or etoposide with BKM120 combination treatment.

- (A)** *PTEN*^{+/+} and *PTEN*^{-/-} HCT116 cells were harvested for cell apoptosis assays after 48 h post-IR treatment with increased gradient doses. Data are represented as mean ± s.d., n = 3, and ***p* < 0.01 (Student's *t*-test)
- (B and C)** *PTEN*^{+/+} or *PTEN*^{-/-} HCT116 cells were pre-treated with/without 1 μM BKM120 for 24 h followed by additional IR (2 Gy) treatment as indicated. 48 h post-irradiation, cells were harvested for cell viability assay **(B)** or cell apoptosis assays **(C)**. Data are shown as mean ± s.d. from three independent experiments. * *p* < 0.05, ***p* < 0.01 (Student's *t*-test)
- (D and E)** The PI3K inhibitor BKM120 did not affect etoposide-induced phosphorylation **(D)** and di-methylation **(E)** of PTEN. IB analysis of anti-HA IPs and WCL derived from U2OS cells transfected with the indicated constructs and where indicated treatment with 30 μM etoposide for 30 min before harvesting.
- (F and G)** The PI3K inhibitor BKM120 did not affect PTEN interaction with MDC1 **(F)** or NSD2 **(G)** upon etoposide treatment. IB analysis of anti-HA IPs and WCL derived from U2OS cells transfected with the indicated constructs and where indicated treatment with 30 μM etoposide for 30 min before harvesting.
- (H)** The PI3K inhibitor BKM120 did not affect the PTEN protein phosphatase activity towards γH2AX *in vitro*. *In vitro* dephosphorylation assay was performed with bacterially purified recombinant GST-tagged PTEN protein incubating with indicated purified γH2AX from HCT116 cells after etoposide treatment, then analyzed by immunoblot analyses.
- (I and J)** The PI3K inhibitor BKM120 slightly promoted the nuclear localization of PTEN in cells. IB analysis of cytoplasm and nuclear part derived from U2OS **(I)** or NIH3T3 **(J)** cells treated with 30 μM etoposide for 30 min before harvesting.
- (K and L)** *PTEN*^{-/-} HCT116 cells reconstituted with the indicated PTEN constructs were pre-treated with 1 μM BKM120 for 24 h followed by additional IR (2 Gy). 48 h post-IR treatment, cells were harvested for apoptosis assays **(K)** or cell viability **(L)**. Data are shown as mean ± s.d. from three independent experiments. * *p* < 0.05 (Student's *t*-test)
- (M and N)** U87MG cells reconstituted with the indicated PTEN constructs were pre-treated with 1 μM BKM120 for 24 h followed by additional IR (2 Gy) **(M)** or etoposide (20 μM) **(N)** treatment for 48 h,

cells were harvested for cell apoptosis assays. Data are represented as mean \pm s.d., $n = 3$, and $*p < 0.05$ (Student's *t*-test).

(O and P) PC3 cells reconstituted with the indicated PTEN constructs were pre-treated with 1 μ M BKM120 for 24 h followed by additional IR (2 Gy) **(O)** or etoposide (20 μ M) **(P)** treatment for 48 h, cells were harvested for cell apoptosis assays. Data are represented as mean \pm s.d., $n = 3$, and $*p < 0.05$ (Student's *t*-test).

(Q) Xenografted tumors as shown in Figure **6J** were dissected after euthanizing the mice and tumors were recorded. Four mice each group.

(R and S) Tumor xenograft assays were performed by subcutaneous injection of *PTEN*^{-/-} HCT116 cells stably expressing shNSD2 or shControl. Tumor growth rate in nude mice treated every other day with etoposide (20 mg/kg) was shown **(R)**. Tumors were dissected and recorded after euthanizing the mice **(S)**. Five mice each group. $*p < 0.05$ (Student's *t*-test).

(T) HCT116 cells were pre-treated with/without 1 μ M BKM120 or 2 μ M DZNep for 24 h followed by additional IR (2 Gy) as indicated. After 48 h post-IR, cells were harvested for cell apoptosis assays. Data are represented as mean \pm s.d., $n = 3$, and $**p < 0.01$ (Student's *t*-test)

(U) HCT116 cells were pre-treated with/without 1 μ M BKM120 for 24 h followed by additional IR (0.5 Gy) and/or 2 μ M DZNep treatment. After one week, cells were stained with crystal violet and the colony number was counted. Data were represented as mean \pm s.d., $n = 3$, and $**p < 0.01$ (Student's *t*-test).

(V) *PTEN*^{+/+} and *PTEN*^{-/-} HCT116 cells were pre-treated with/without 1 μ M BKM120 24 h followed by additional etoposide (20 μ M) and/or 2 μ M DZNep as indicated. 48 h post treatment, cells were harvested for cell viability and apoptosis assays. Data are represented as mean \pm s.d., $n = 3$, $*p < 0.05$ and NS indicates no significant difference (Student's *t*-test).

(W) *PTEN*^{+/+} and *PTEN*^{-/-} HCT116 cells were pre-treated with/without 1 μ M BKM120 for 24 h followed by additional etoposide (20 μ M) or 2 μ M DZNep as indicated. 24 h post treatment, cells were replaced with fresh medium. After one week, cells were stained with crystal violet and the colony number was counted. Data are represented as mean \pm s.d., $n = 3$, $*p < 0.05$ and NS indicates no significant difference (Student's *t*-test).

(X) Xenograft tumors in Figure **6I** were dissected after euthanizing the mice and tumors were recorded. Four mice each group.

(Y) A schematic representation of how PTEN methylation and protein phosphatase activity responding to DNA damage signaling. In addition to suppressing PI3K/Akt signaling through the lipid phosphatase activity in the cytoplasm, PTEN also exerts its protein phosphatase activity to control DNA damage repair in the nucleus. Upon DNA damage, the NSD2 methyltransferase promotes the methylation of PTEN, which is recruited into DNA damage sites to help complete DNA damage repair through dephosphorylating γ H2AX.