Supplemental Materials and Methods

Cell culture. MCF-10A cells were cultured in DMEM/F12 medium supplemented with 5% horse donor serum. To generate inducible LacZ-knockdown cell lines, pBabe-H1-siLacZ was transfected into MCF7 (MCF7-TR-7) or RKO (RKO-TR-13) cells and the inducible expression of siRNA against LacZ was confirmed by the reduced expression of HA-tagged LacZ in cells transfected with pcDNA3-HA-LacZ.

Plasmids. Ha-tagged LacZ cDNA (GenBank #BC112941) was amplified by PCR from an *E.coli* with forward primer, 5'-AAGCTT ACC ATG tac cca tac gac gta cca gat tac gct GAG TTC CTG CAC TGG ATG G -3', and reverse primer, 5'- CTC GAGTTA TTT TTG ACA CCA GAC CAA C -3'. The HA-tagged LacZ cDNA was then cloned into pcDNA3 and used for transient LacZ expression.

To generate a construct that expresses a siRNA against LacZ under the control of the tetracycline-regulated H1 promoter, two 64-base oligos were annealed and then cloned into pBabe-H1 siRNA expression vector, and the resulting plasmid designed pBabe-H1-siLacZ. The sense oligo is 5'-GAT CCC CTT TAA CCG CCA GTC AGG CTT TCA AGA GAA GCC TGA CTG GCG GTT AAA TTT TTG GAA A -3', and the antisense oligo is 5'-AGC TTT TCC AAA AAT TTA ACC GCC AGT CAG GCT TCT CTT GAA AGC CTG ACT GGC GGT TAA AGG G-3'.

Double-strand siRNA sequence. The scrambled double-strand siRNA sequence used in supplemental Fig. 3 is GCA GUG UCU CCA CGU ACU A. The double-strand siRNA sequence against GPR87 is GCA UCU UGC UGA AUG GUU U.

Antibodies. Anti-p-AKT (Ser-473) and anti-AKT were purchased from Cell Signaling.

Supplemental Figure Legends

Supplementary Figure 1. Knockdown of LacZ has no effect on GPR87 expression and cell growth. (*A*) Left panel: generation of RKO and MCF7 cell lines that inducibly express a siRNA against LacZ. The expression of inducible siRNA against LacZ was confirmed by reduced expression of HA-tagged LacZ in cells transfected with pcDNA3-HA-LacZ. Right panel: the levels of GPR87 transcripts was examined in RKO and MCF7 cells uninduced or induced to express a siRNA against LacZ for 72 h. (*B*) Colony formation assays were performed with RKO (left panel) and MCF7 (right panel) cells uninduced (control) or induced (LacZ-KD) to express a siRNA against LacZ along with mock-treatment (Ctrl) or treatment with 10 ng/mL of doxorubicin or treatment with 10 nM of camptothecin (CPT) over a 14-day period. (*C*)Western blot analysis was performed to measure the level of p53 in RKO and MCF7 cells uninduced (-) or induced (+) to express a siRNA against LacZ for 72 h, followed by mock-treatment (Ctrl) or treatment with 250 ng/mL of doxorubicin (Dox) or 250 nM camptothecin (CPT) for 24 h. GAPDH was used as loading control.

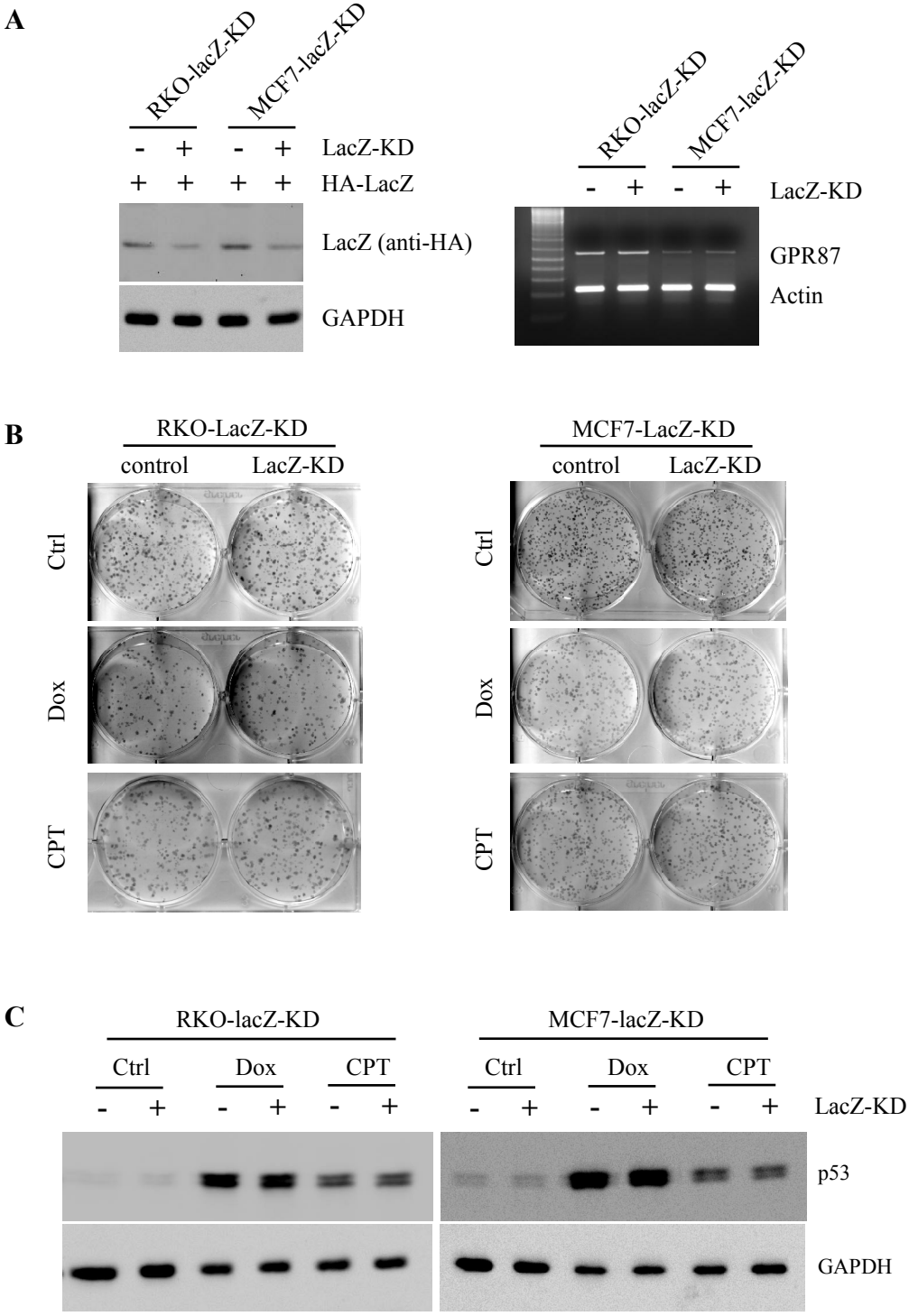
Supplementary Figure 2. The effect of GPR87-knockdown on cell proliferation is not cell type-specific. (*A*) RT-PCR was performed to measure the levels of GPR87 transcripts in GPR87-knockdown MCF7 cells (clone #43) upon induction of siRNA for 3 days. (*B*) GPR87 knockdown enhances DNA damage-induced growth inhibition. Left panel: colony formation assay was performed with MCF7 cells (clone #43), which were uninduced (control) or induced (GPR87-KD) to express siRNA against GPR87 along with mock-treatment (Ctrl) or treatment with 10 ng/mL of doxorubicin (Dox) or 10 nM camptothecin (CPT), and then cultured over a 14-day period. Right panel: the average number of colonies for each treatment condition was calculated from three separate experiments. (*C*) Western blots were prepared using extracts from

MCF7 cells that were uninduced (-) or induced (+) to knock down GPR87 for 3 d, followed by mock-treatment (Ctrl) or treatment with 250 ng/mL of doxorubicin (Dox) or 250 nM camptothecin (CPT) for 24 h. The blots were probed with antibodies against p53, p21, Mdm2, PARP, and actin, respectively.

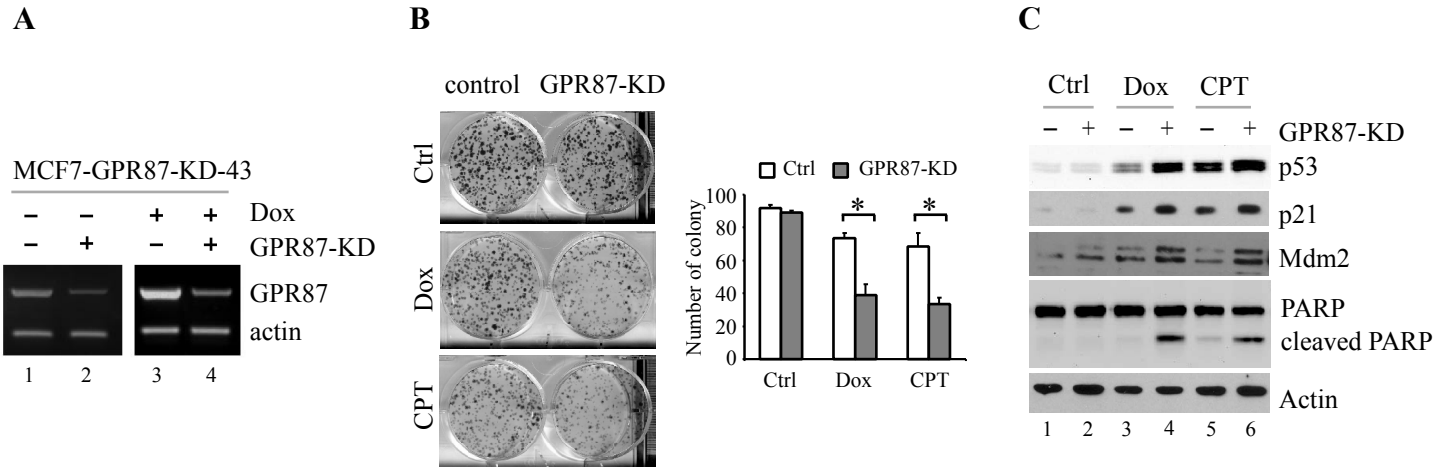
Supplementary Figure 3. GPR87 knockdown enhances DNA damage-induced p53 activation and induction of p21 in immortalized MCF10A cells. *(A)* MCF-10A cells were transiently transfected with scramble siRNA or siRNA against GPR87 for 3 days along with mock-treatment or treatment with 250 ng/mL of doxorubicin (Dox) for 24 h. The level of GPR87 transcripts was measured by RT-PCR. (*B*) Western blots were prepared using extracts from MCF-10A cells that were transiently transfected with scramble siRNA or siRNA against GPR87 for 3 d, followed by mock-treatment (Ctrl) or treatment with 250 ng/mL of doxorubicin (Dox) or 250 nM camptothecin (CPT) for 24 h. The blots were probed with antibodies against p53, p21, and GAPDH, respectively.

Supplementary Figure 4. DNA damage-induced Akt activation is inhibited by GPR87 knockdown. Western blots were prepared with extracts from RKO cells that were uninduced (-) or induced (+) to knock down GPR87 for 3 d, followed by mock-treatment or treatment with 250 ng/mL of doxorubicin (Dox) for 5-30 min. The blots were probed with antibodies against AKT, phosphorylated AKT, and GAPDH, respectively.

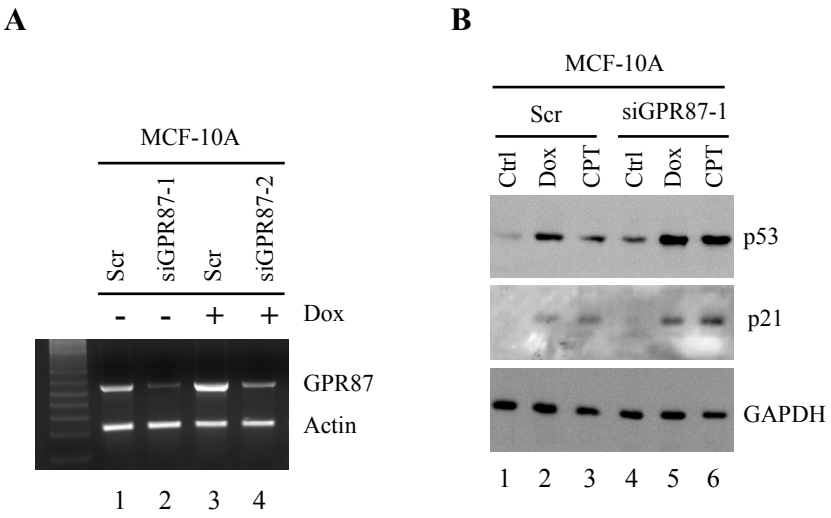
Supplementary Figure 1



Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4