Supplementary Information Appendix:

Supplementary figures and tables

Supplementary materials and methods

Supplementary figures and tables

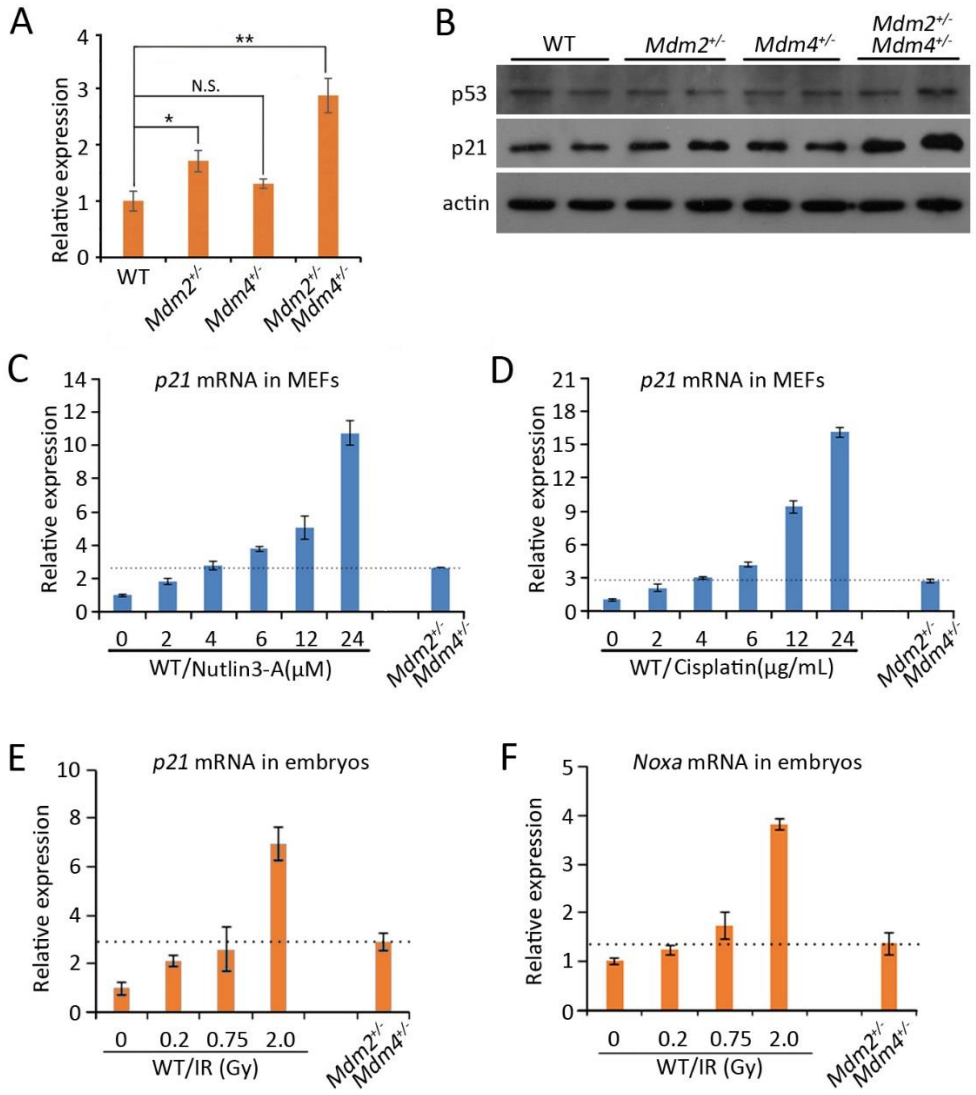

Fig. S1. Mild p53 activation in *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ MEFs and embryos.

(A)QRT-PCR analysis of *p21* mRNA expression in WT, *Mdm2*$^{+/-}$, *Mdm4*$^{+/-}$ *and* *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ MEFs (n=3). Data are presented as Mean±SD. *p≤0.05, **p≤0.01 (one-way ANOVA followed by Tukey's test).

(B) Western blot of p21 protein in WT, *Mdm4*$^{+/-}$, *Mdm2*$^{+/-}$, *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ MEFs.

(C) QRT-PCR analysis of *p21* mRNA expression in WT MEFs treated with different doses of Nutlin3-A as compared to the untreated *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ MEF. Error bar indicates SD.

(D) QRT-PCR analysis of *p21* mRNA expression in WT MEFs treated with different doses of Cisplatin as compared to the untreated *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ MEF. Error bar indicates SD.

(E) QRT-PCR analysis of *p21* mRNA expression in E12.5 WT embryos treated with different doses of X-Ray irradiation as compared to the untreated E12.5 *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ embryos. Error bar indicates SD.

(F) QRT-PCR analysis of *Noxa* mRNA expression in E12.5 WT embryos treated with different doses of X-Ray irradiation as compared to the untreated E12.5 *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ embryos. Error bar indicates SD.

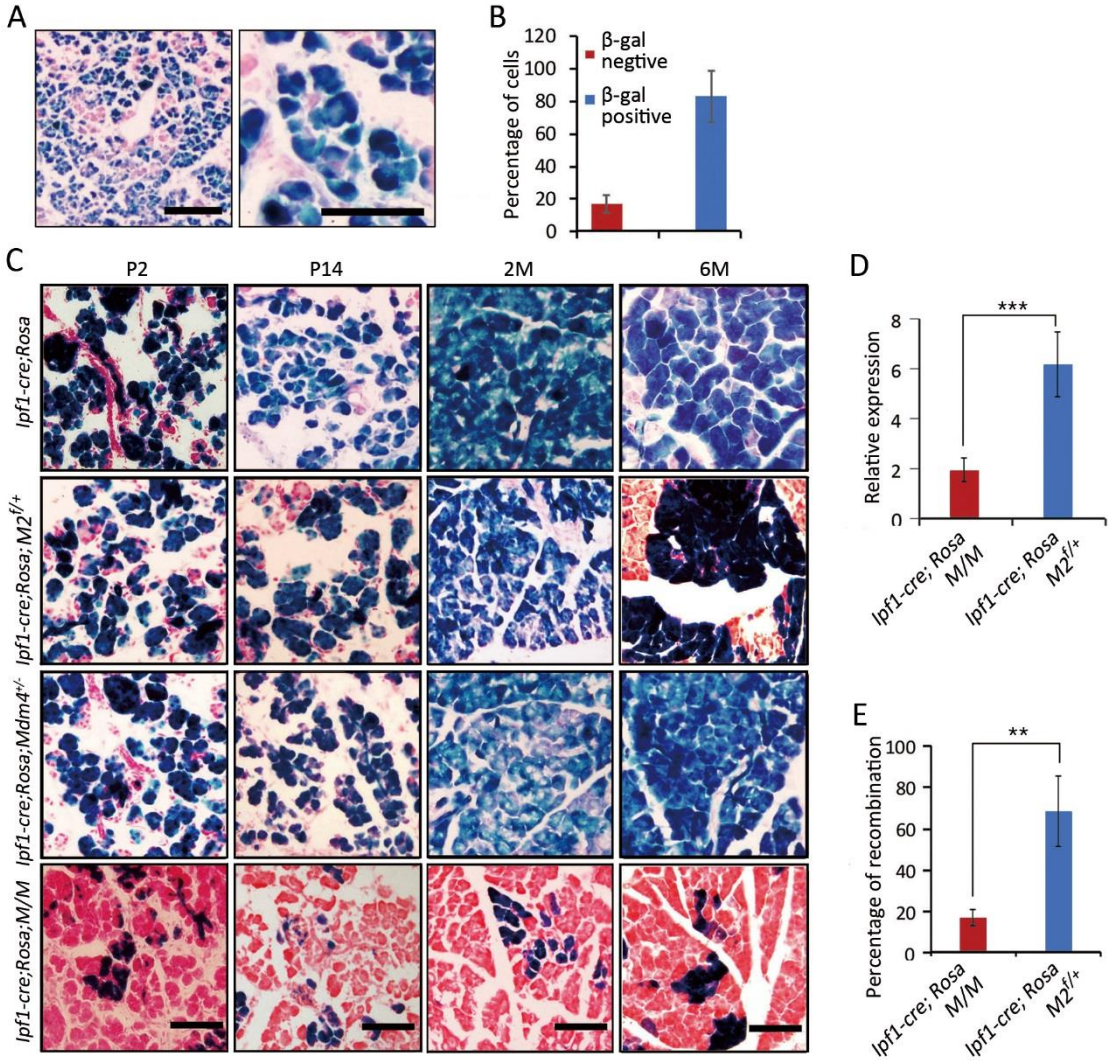

Fig.S2. *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ cells were dramatically reduced in mosaic pancreatic tissue

(A) X-gal staining of frozen section of the pancreas from adult *Ipf1-cre; Rosa-lacZ* mice. Scale bar (left) represents 200um; scale bar (right) represents 100μm.

(B) Quantification of the β-gal expressing cells in pancreas of adult *Ipf1-cre; Rosa-lacZ* mice (n=3). Data are presented as Mean±SD.

(C) X-gal staining of the frozen sections of pancreas from *Ipf1-cre; Rosa-lacZ*, *Ipf1-cre; Rosa-lacZ; Mdm2*$^{flox/+}$, *Ipf1-cre; Rosa-lacZ; Mdm4*$^{+/-}$ and *Ipf1-cre; Rosa-lacZ; M/M* mice. *M2* means *Mdm2*. Scale bars represent 100μm.

(D) QRT-PCR analysis of *LacZ* levels in pancreas of 6-8 week-old *Ipf1-cre; Rosa-lacZ; Mdm2*$^{flox/+}$ and *Ipf1-cre; Rosa-lacZ; M/M* mice (n=4). *M2* means *Mdm2*. Data are presented as Mean±SD. ***p≤0.001 (two-tailed t test).

(E) Q-PCR analysis of the recombined *Mdm2* locus in genomic DNA from pancreas of 6-8 week-old *Ipf1-cre;Rosa-lacZ; Mdm2*$^{flox/+}$ and *Ipf1-cre;Rosa-lacZ;M/M* mice (n=4). *M2* means *Mdm2.* Data are presented as Mean±SD. **p≤0.01 (two-tailed t test).

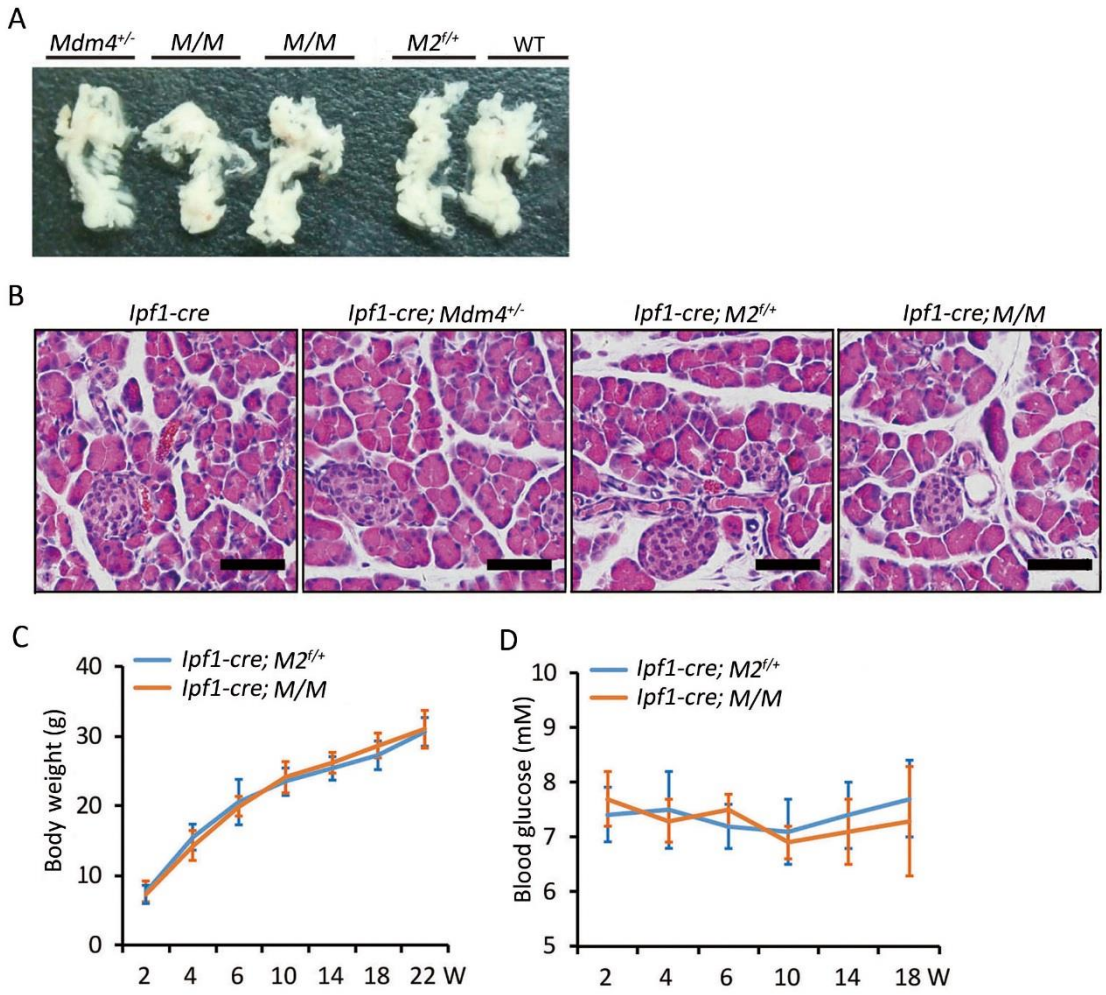

Fig. S3. Normal histology and function of pancreas in *Ipf1-cre; M/M* mice.

(A) Images of pancreas from two week-old *Ipf1-cre* (WT), *Ipf1-cre; Mdm2*$^{flox/+}$ (*Mdm2*$^{flox/+}$), *Ipf1-cre; Mdm4*$^{+/-}$ (*Mdm4*$^{+/-}$) and *Ipf1-cre; M/M* (*M/M*) mice. *M2* means *Mdm2*.

(B) H&E staining of the sections of pancreas from two week-old *Ipf1-cre;M/M*, *Ipf1-cre;Mdm2*$^{flox/+}$, *Ipf1-cre;Mdm4*$^{+/-}$ and *Ipf1-cre* mice. *M2* means *Mdm2.* Scale bar represents 100μm.

(C) Body weight growth of *Ipf1-cre; Mdm2*$^{flox/+}$ (n=9) and *Ipf1-cre; M/M* mice (n=7) from 2 weeks to 22 weeks after birth. *M2* means *Mdm2*. Data are presented as mean±SD.

(D) Blood glucose levels of *Ipf1-cre; Mdm2*$^{flox/+}$ (n=9) and *Ipf1-cre; M/M* mice (n=7) between 2-week to 18-week of age after birth. *M2* means *Mdm2*. Data are presented as mean±SD.

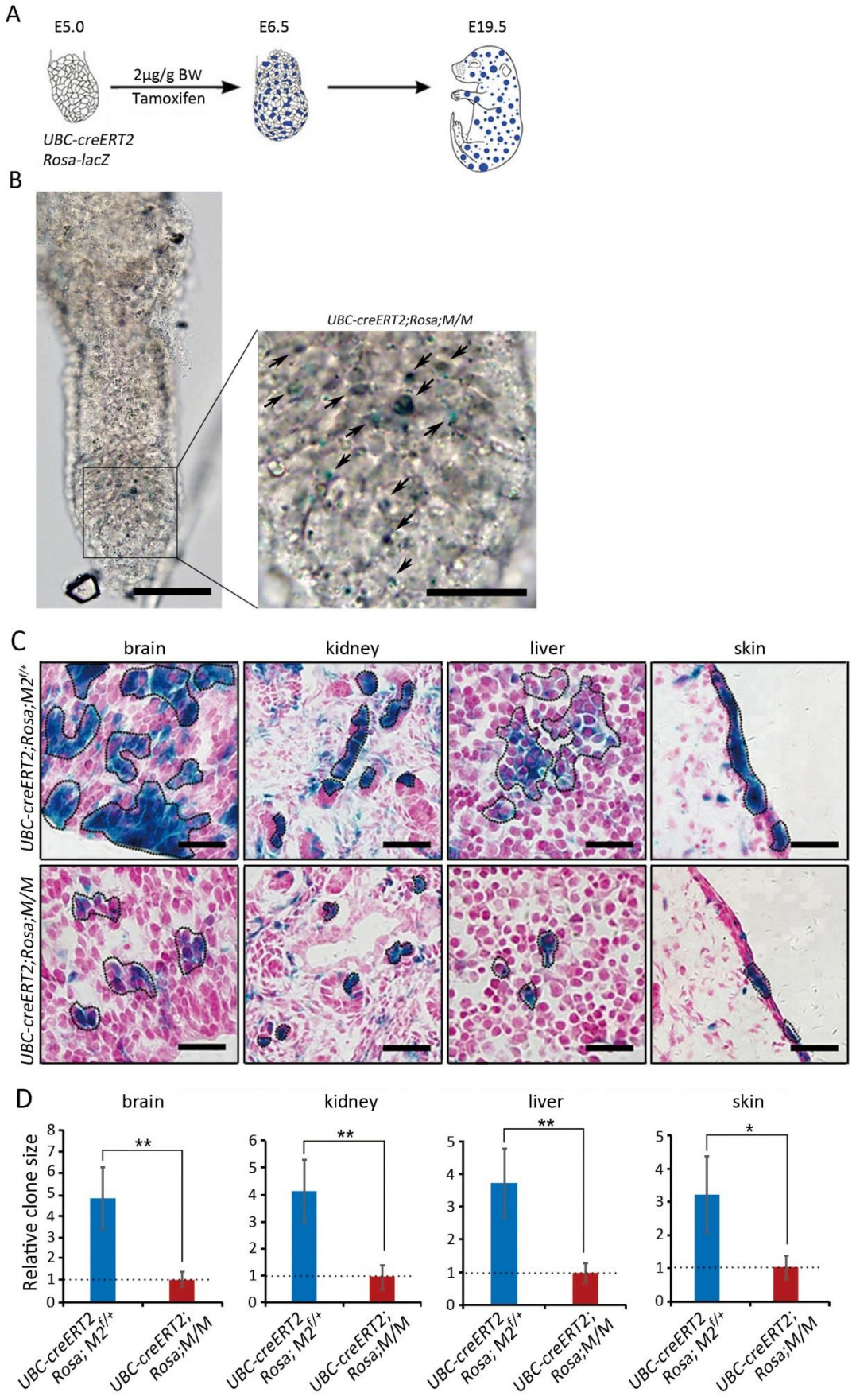
A
E5.0
E6.5
E19.5
2μg/g BW
Tamoxifen
UBC-creERT2
Rosa-lacZ
B
UBC-creERT2;Rosa;M/M
C
brain
kidney
liver
skin
UBC-creERT2;Rosa;M2f/+
UBC-creERT2;Rosa;M/M
D
brain
kidney
liver
skin
Relative clone size
**
**
**
*
UBC-creERT2 Rosa; M2f/+
UBC-creERT2; Rosa;M/M

Fig.S4. Clonal analysis showed growth disadvantages of the cells with the *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ genotype in mosaic embryos.

(A) A schematic diagram for clonal analysis. BW: body weight.

(B) Single cell labeling at early stage embryos of *UBC-creERT2; Rosa-lacZ; M/M* mice. Tamoxifen (2μg per bodyweight gram) was injected to pregnant mice with E5.0 embryos. Thirty-six hours later, the embryos were collected and processed to whole-mount X-gal staining (left). Right panel represents a higher magnification of the boxed area in the left panel. Arrows indicated β-gal positive cells. Scale bar (left) represents 0.5mm; scale bar (right) represents 200μm.

(C) X-gal staining of brain, kidney, liver and skin from E19.5 *UBC-creERT2; Rosa-lacZ; Mdm2*$^{flox/+}$ and *UBC-creERT2; Rosa-lacZ; M/M* embryos. Areas marked by dotted lines indicated cell clones. *M2* means *Mdm2*. Scale bars represent 100μm.

(D) Quantifications of the clone size derived from *UBC-creERT2; Rosa-lacZ; Mdm2*$^{flox/+}$ and *UBC-creERT2; Rosa-lacZ; M/M* mice (n=3). *M2* means *Mdm2*. Data are presented as Mean±SD. *p≤0.05, **p≤0.01 (two-tailed t test).

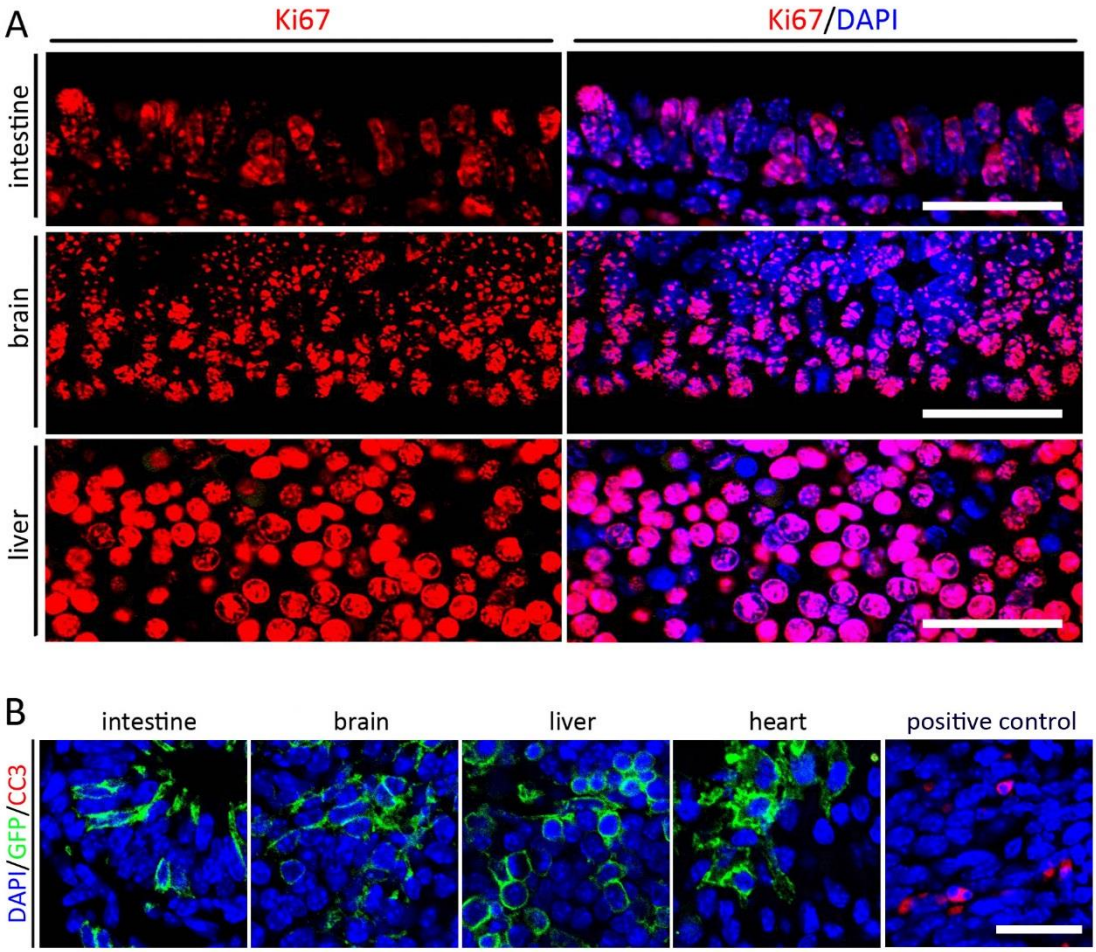

Fig. S5. Analyses of proliferation in *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ embryos and apoptosis in *UBC-creERT2; Rosa-mTmG*; *M/M* embryos, respectively.

(A) Immunofluorescent staining of Ki67 in intestine, brain and liver of E12.5 *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ embryos. Scale bar represents 50μm.

(B) Immunofluorescent staining of cleaved-Caspase3 (CC3) and GFP in intestine, brain, liver and heart of the E12.5 *UBC-creERT2; Rosa-mTmG*; *M/M* embryos. GFP was used to mark the cells with the *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ genotype. E12.5 WT embryos (brain) treated with 2.0Gy X-Ray irradiation were used as positive control. Scale bar represents 50μm.

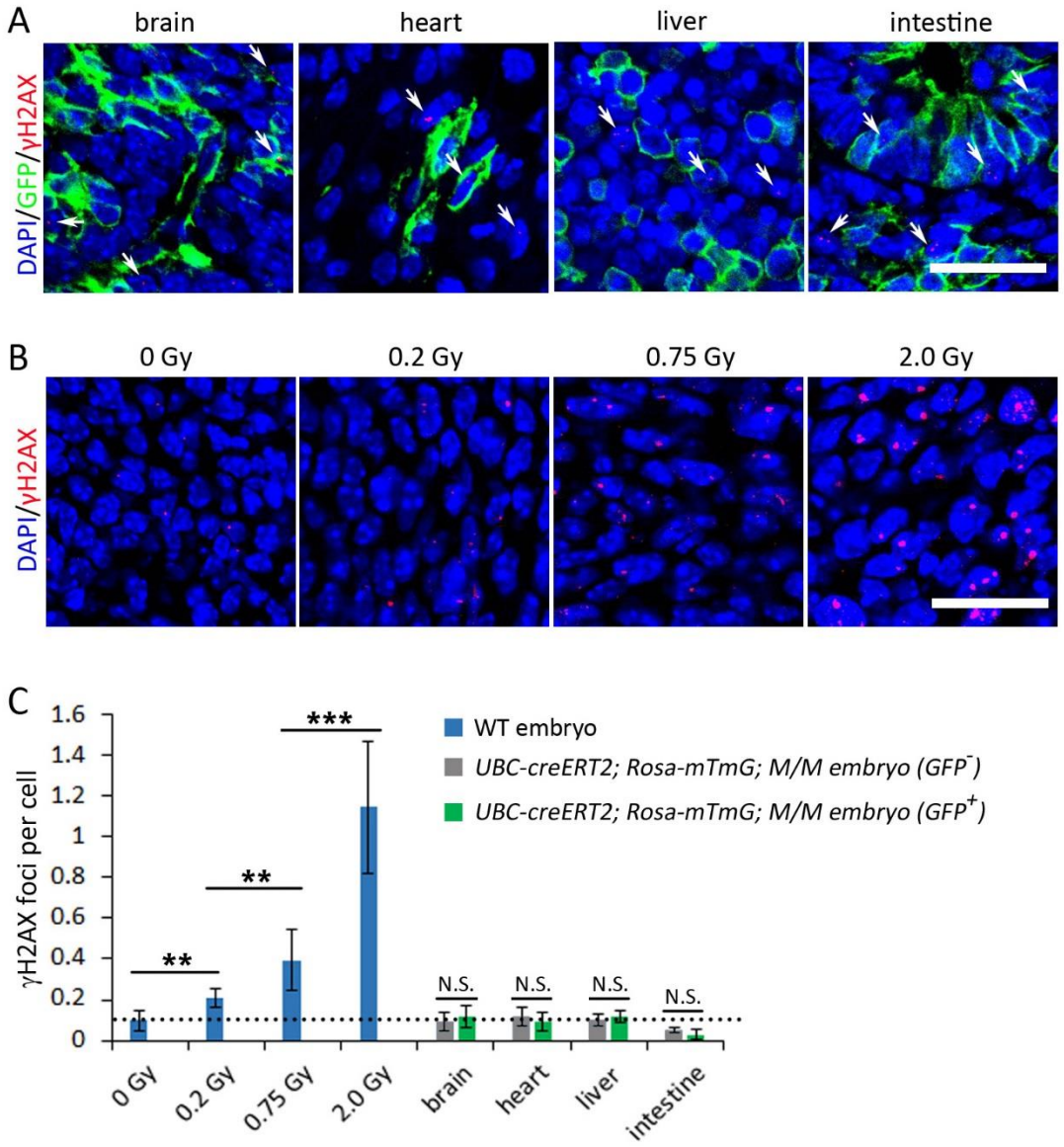

Fig. S6. Analysis of DNA damage in *UBC-creERT2; Rosa-mTmG*; *M/M* mosaic embryos.

(A) Immunofluorescent staining for γ-H2AX and GFP in brain, heart, liver and intestine of the E12.5 *UBC-creERT2; Rosa-mTmG*; *M/M* embryos. GFP was used to mark the cells with the *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ genotype. Arrows indicated γ-H2AX positive foci. Scale bar represents 50μm.

(B) Immunofluorescent staining for γ-H2AX in brain of X-Ray irradiated E12.5 WT embryos. Scale bar represents 50μm.

(C) Quantification of γ-H2AX positive foci in cells of X-Ray irradiated E12.5 WT embryos, and GFP-positive and negative cells of the low-dose tamoxifen treated *UBC-CreERT2; Rosa-mTmG; M/M* embryos. Data are presented as Mean±SD. *p≤0.05, **p≤0.01, ***p≤0.001 (one-way ANOVA followed by Tukey's test). N.S. means no significance.

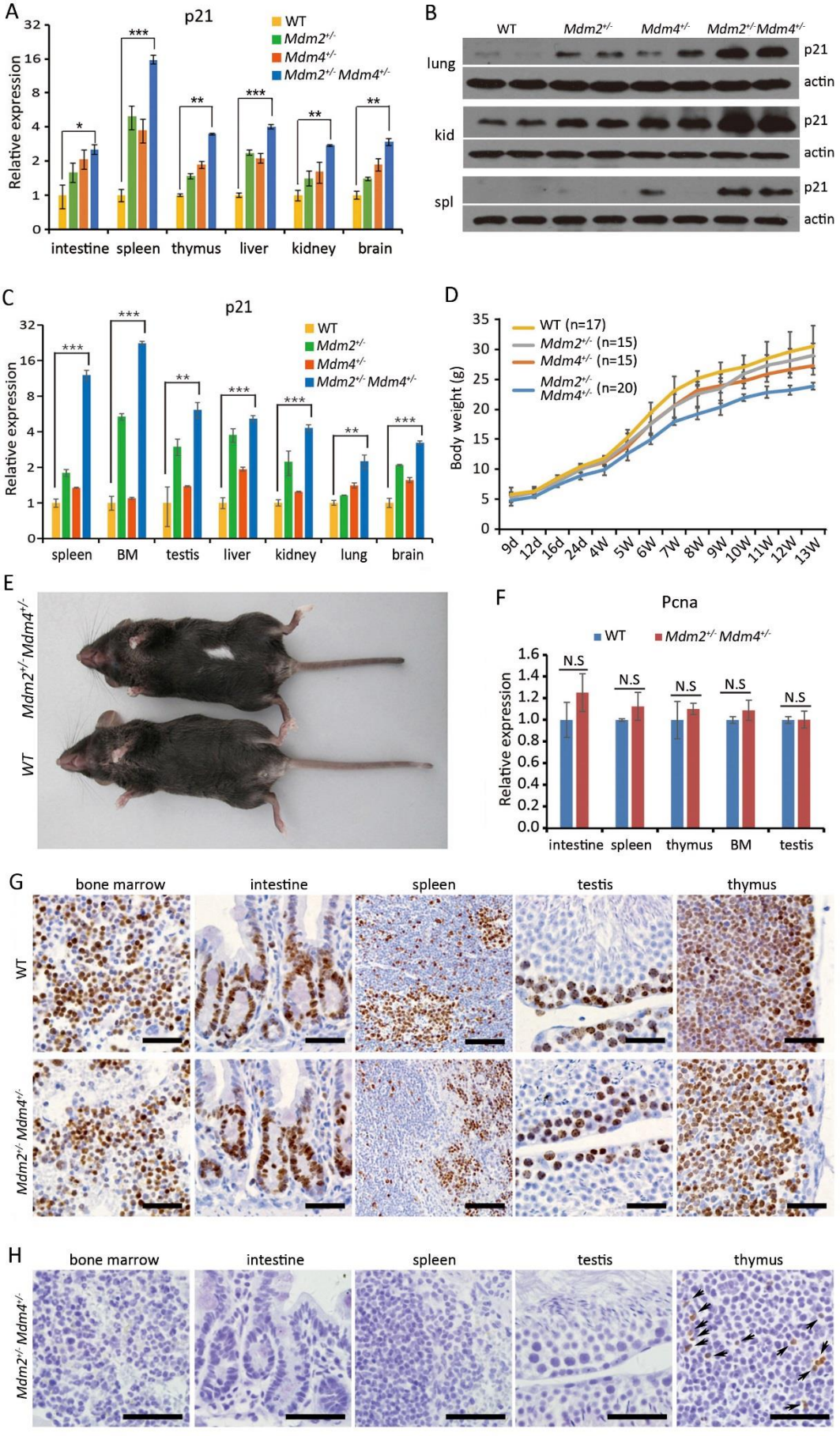
A
p21
WT
Mdm2+/-
Mdm4+/-
Mdm2+/- Mdm4+/-
Relative expression
intestine
spleen
thymus
liver
kidney
brain
B
WT
Mdm2+/-
Mdm4+/-
Mdm2+/- Mdm4+/-
lung
kid
spl
p21
actin
C
p21
spleen
BM
testis
liver
kidney
lung
brain
D
WT (n=17)
Mdm2+/- (n=15)
Mdm4+/- (n=15)
Mdm2+/- Mdm4+/- (n=20)
Body weight (g)
9d
12d
16d
24d
4W
5W
6W
7W
8W
9W
10W
11W
12W
13W
E
Mdm2+/- Mdm4+/-
WT
F
Pcna
WT
Mdm2+/- Mdm4+/-
N.S
intestine
spleen
thymus
BM
testis
G
bone marrow
intestine
spleen
testis
thymus
WT
Mdm2+/- Mdm4+/-
H
bone marrow
intestine
spleen
testis
thymus
Mdm2+/- Mdm4+/-

Fig.S7. *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice were able to tolerate mild p53 activation.

(A) Relative expression of *p21* mRNA in neonatal tissues of WT, *Mdm2*$^{+/-}$, *Mdm4*$^{+/-}$ and *Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$ mice (n=4). Data are representative of four independent experiments. Error bar indicates Mean±SD. *p≤0.05, **p≤0.01, ***p≤0.001 (one-way ANOVA followed by Tukey's test).

(B) Western blot analysis of p21 protein in lung, kidney and spleen of neonatal WT, *Mdm2*$^{+/-}$, *Mdm4*$^{+/-}$ and *Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$ mice (n=2). kid, kidney; spl, spleen.

(C) Relative expression of *p21* mRNA in spleen, bone marrow (BM), testis, liver, kidney, lung and brain of adult WT, *Mdm2*$^{+/-}$, *Mdm4*$^{+/-}$ and *Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$ mice (n=4). Data are representative of four independent experiments. Error bar indicates Mean±SD. **p≤0.01, ***p≤0.001 (one-way ANOVA followed by Tukey's test).

(D) Body weight growth of WT, *Mdm2*$^{+/-}$, *Mdm4*$^{+/-}$ and *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice. Data are presented as Mean±SD.

(E) Photographs of 10 week-old WT and *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice.

(F) Relative expression of *Pcna* mRNA in small intestine, spleen, thymus, bone marrow (BM) and testis of adult WT and *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice (n=4). Data are presented as mean±SD. Statistical significance was determined by Student's two-tailed t test. N.S. meansnot significant.

(G) Immunohistochemical analysis for Ki67 in bone marrow, intestine, spleen, testis and thymus of adult WT and *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice. Scale bar represents 100μm.

(H)Immunohistochemical analysis for cleaved-Caspase3 in bone marrow, intestine, spleen, testis and thymus of adult *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ mice. Arrows indicated apoptotic cells. Scale bar represents 100μm.

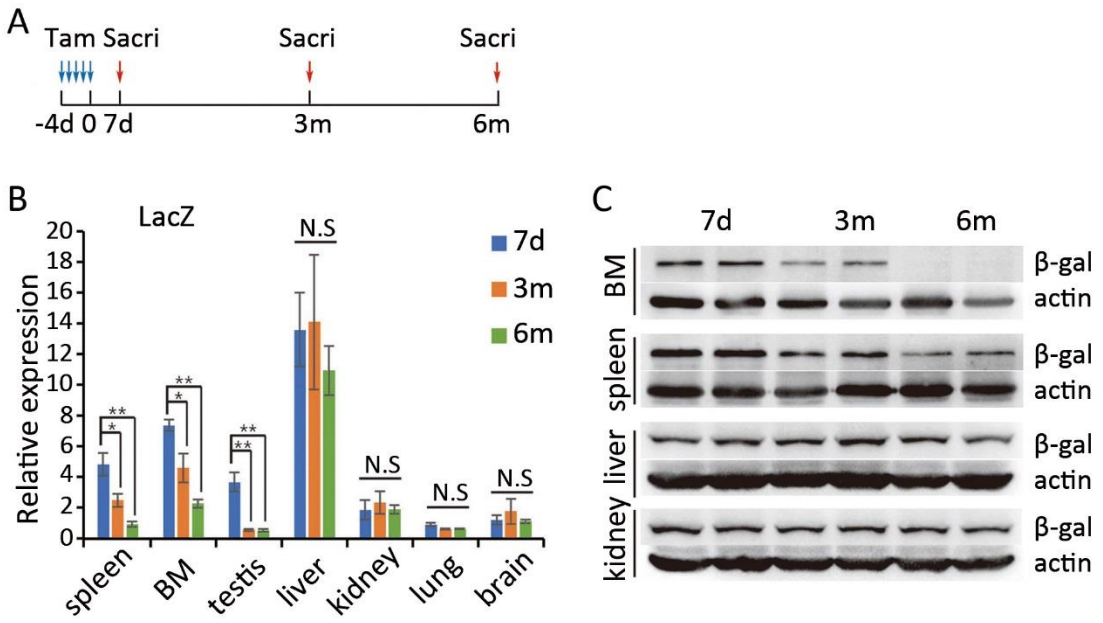

Fig.S8. Gradual reduction of the cells with the *Mdm2*$^{+/-}$*Mdm4*$^{+/-}$ genotype in fast turnover tissues of the adult mosaic mice.

(A) A scheme to generate mosaicism in adult mice.

(B) *LacZ* levels in tissues collected at indicated time points from tamoxifen-treated adult *UBC-creERT2;Rosa-lacZ;M/M* mice (n=2). Data are presented as Mean±SD. *p≤0.05, **p≤0.01 (one-way ANOVA followed by Tukey's test). N.S. means not significant.

(C) Western blot analysis of β-gal protein in tissues collected at indicated time points from tamoxifen-treated adult *UBC-creERT2; Rosa-lacZ; M/M* mice (n=2).

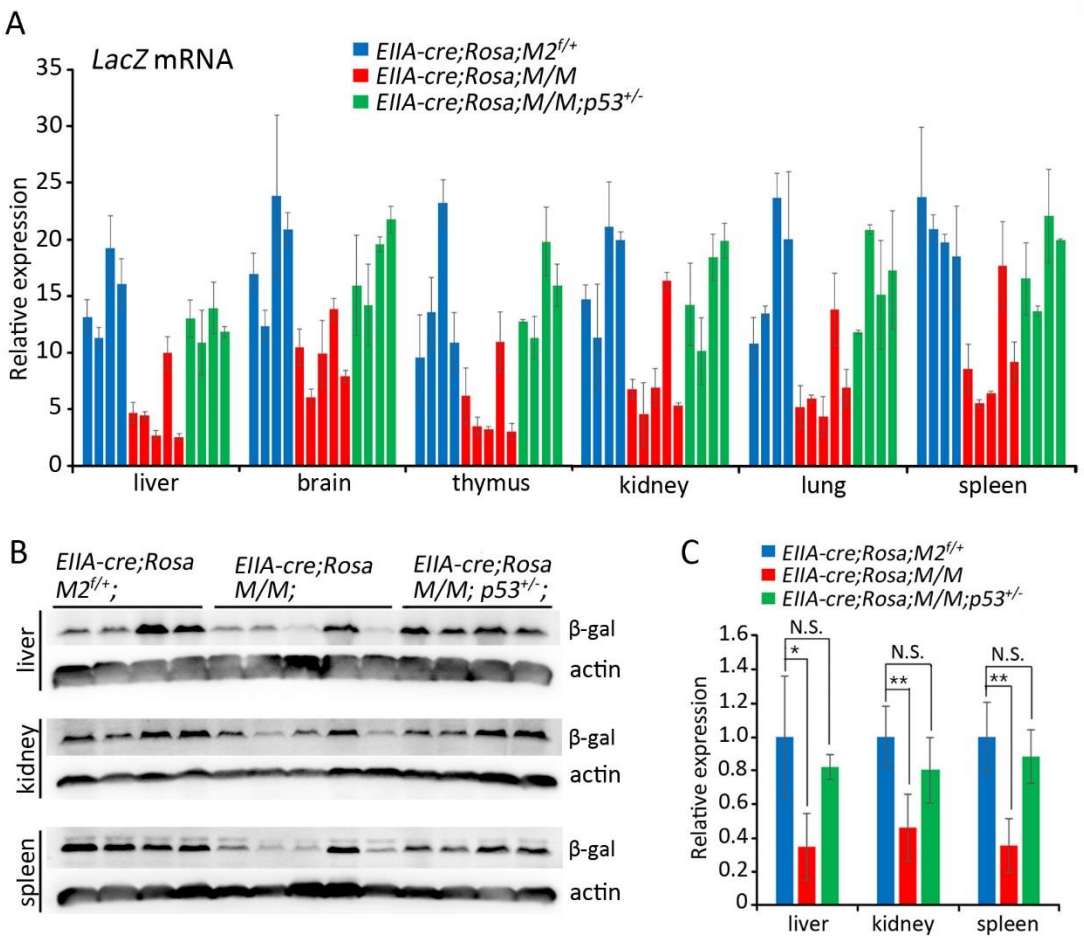

Fig. S9. The loss of β-gal expression in the *EIIA-cre; Rosa-lacZ; M/M* mosaic mice was rescued by deleting one copy of *p53* gene.

(A) QRT-PCR analysis of *LacZ* levels in liver, brain, thymus, kidney, lung and spleen of neonatal *EIIA-cre; Rosa-lacZ; Mdm2$^{flox/+}$* (n=4), *EIIA-cre; Rosa-lacZ; M/M* (n=5) and *EIIA-cre; Rosa-lacZ; M/M*; *p53$^{+/-}$* (n=4) mice. *M2* means *Mdm2*. Data are presented as Mean±SD.

(B) Western blot analysis of β-gal protein in liver, kidney and spleen of P0 *EIIA-cre; Rosa-lacZ; Mdm2$^{flox/+}$* (n=4), *EIIA-cre; Rosa-lacZ; M/M* (n=5) and *EIIA-cre; Rosa-lacZ; M/M*; *p53$^{+/-}$* (n=4) mice. *M2* means *Mdm2*.

(C) Quantification of β-gal protein levels detected by Western blot in (B). *M2* means *Mdm2*. Data are presented as Mean±SD. *p≤0.05, **p≤0.01 (one-way ANOVA followed by Tukey's test). N.S means not significant.

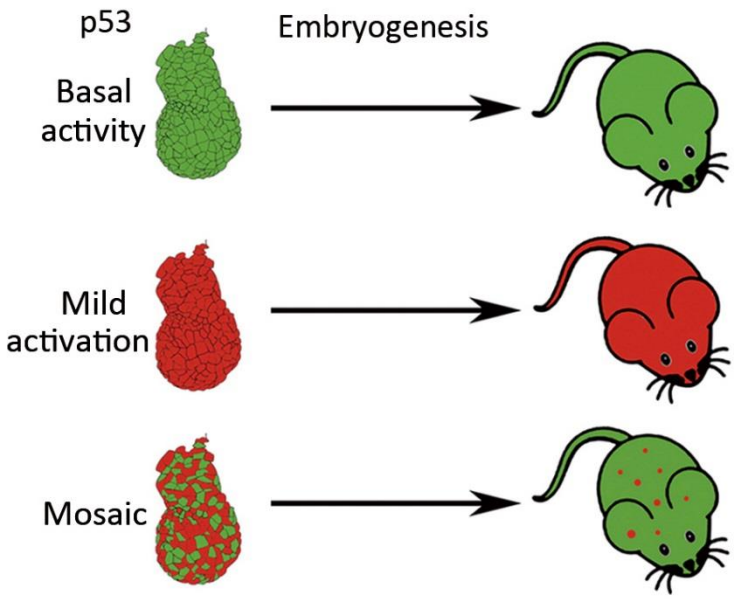

Fig. S10. A model illustrating the distinct fate of cells with mild p53 activation in different multi-cellular contexts.

Supplementary Table 1. Genetic background analysis of *Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$ and *UBC-creERT2; Rosa-LacZ; M/M* mice.

Ref SNP ID	Chr#	C57BL/6J	129S1/SvlmJ	*Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$			*UBC-creERT2;Rosa;M/M*		
				1#	2#	3#	1#	2#	3#
rs3022883	2	A	C	A	A	A	A/C	A/C	A/C
rs3022953	3	T	C	T	T	T	T	T	T
rs3022977	4	C	T	C	C	C	C	C	C
rs3023064	6	G	T	G	G	G	G/T	G	G
rs3023106	7	T	G	T/G	T/G	T/G	T	T	T
rs3023177	8	C	A	C	C	C	C	C	C
rs3023251	11	T	C	T	T	T	T	T	T
rs3023342	12	T	C	T	T	T	T	T	T
rs3023382	13	T	G	T	T	T	T	T	T
rs3091174	15	G	A	G	G	G	G	G	G
rs3023436	16	A	T	A	A	A	A	A	A
rs3089604	X	T	C	T	T	T	T	T	T

Supplementary Table 2. A summary of the data from genetic background analysis shown inSupplementary Table 1.

Mice	*Mdm2*$^{+/-}$ *Mdm4*$^{+/-}$			*UBC-creERT2;Rosa;M/M*		
	1#	2#	3#	1#	2#	3#
Degree of C57BL/6J background (%)	95.8	95.8	95.8	91.6	95.8	95.8
Average (%)		95.8			94.4	

Supplementary materials and methods

Genotyping. For the early embryos, One Step Mouse Genotyping Kit (Vazyme) was used to facilitate the genotyping. In brief, the stained embryos were lysed and the lysis was then used directly for genotyping.

Genomic DNA of postnatal mice was isolated from toes and tail tips after the treatment with Proteinase K. All genotyping was performed by PCR based on the following condition: one step at 94 °C for 3 min, followed by 35 cycles at 94 °C for 30 s, 56 °C for 30 s, 72 °C for 90 s, then one step at 72 °C for 5min, and finally maintained at 16°C. Primers used for each genotyping reaction were described below.

Gene	Primer name	Primer sequence	Band size
Cre	Cre-F	AATGCTTCTGTCCGTTTGC	Cre: 712bp
	Cre-R	ACCAGAGTCATCCTTAGCG	
Mdm2^{KO}	O'mdm4	ATCTGAGAGCTCGTGCCCTTCG	KO: 300bp
	O'mdm20	TGTGGCTGGAGCATGGGTATTG	WT:400bp
	Neo3'd	GGCGGAAAGAACCAGCTGGGGC	
Mdm2^{flox}	Fm-a	TGTGGAGAAACAGTTACTTC	Flox:474bp
	Fm-b	CTGTGCTCCTTCACAGAG	WT: 342bp
Mdm4^{KO}	In2re	TTTCCAGAGACATGTTATTATGAC	KO: 527bp
	F4	TAGAATCTGGAATTACAGACAG	WT: 300bp
p53^{KO}	0036	ACAGCGTGGTGGTACCTTAT	KO: 650bp
	0037	TATACTCAGAGCCGGCCT	WT: 450bp
	0038	CTATCAGGACATAGCGTTGG	
Rosa-LacZ	Rosa-1	AAAGTCGCTCTGAGTTGTTAT	LacZ:300bp
	Rosa-2	GCGAAGAGTTTGTCCTCAACC	WT: 630bp
	Rosa-3	GGAGCGGGAGAAATGGATATG	
Rosa-mTmG	TG-1	CTCTGCTGCCTCCTGGCTTCT	TG: 250bp
	TG-2	CGAGGCGGATCACAAGCAATA	WT:330bp

TG-3	TCAATGGGCGGGGGTCGTT

Regents. Tamoxifen (Sigma) solution was prepared by dissolving in ethanol at concentration of 100mg/ml. Then, corn oil (Sigma) was added to the solution to make 10mg/g Tamoxifen solution in a mixture of 90% corn oil and 5% ethanol and delivered into pregnant mice by intraperitoneal injection at 30μg or 2μg per gram of total bodyweight as specified. Meanwhile, progesterone (Sigma) was administered at a half dose of tamoxifen to prevent early abortion. One hundred and fifty micrograms of tamoxifen per gram of total body weight was administered intraperitoneally to adult *UBC-creERT2* mice every other day for five times. Nutlin3-A (Sigma) was dissolved in DMSO at concentration of 5mM as stock solution. Cisplatin (Beyotime) was stocked at -20°C as powder. The solution was prepared freshly by dissolving the powder with DMSO at concentration of 6mg/ml.

Immunohistochemistry and immunofluorescence. Tissues were dissected and fixed in ice-cold 4% PFA overnight, transferred to gradient alcohol (from 50% to 100%), then embedded in paraffin. Six-micrometer sections were cut. After deparaffinized and rehydrated, slices were processed to heat-induced epitope retrieval with sodium citrate (pH 6.0), then were blocked with normal goat serum for half an hour at room temperature. For immunohistochemistry, slices were incubated with primary antibody, then biotin-tagged secondary antibodies followed by avidin-tagged horseradish peroxidase (HRP). Signals were developed with DAB agents (MaiXinBio) and then co-stained with hematoxylin. For immunofluorescence, after incubation with primary antibodies, the slices were treated with fluorophore-tagged secondary antibodies. Finally, slices were mounted with 50% glycerol and images were obtained from a confocal microscope (Olympus FV1000).

Western blotting. Tissues and MEFs were lysed in RIPA buffer (150mM sodium chloride, 1.0% NP-40 or Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS, 50mM Tris, pH 8.0) supplemented with complete Protease Inhibitor Cocktail Tablets (Roche). The protein lysates were denatured and then loaded to the PAGE gel. After transfer, the membrane was blocked with 5% non-fat milk dissolved in 0.1% TBST for 30-60mim which is followed by incubation with primary antibody diluted in 5% non-fat milk overnight at 4℃ or 2h at room temperature. After washed with TBST 5min each for three times, the membrane was incubated with secondary antibodies linked with HRP at room temperature for 2 hours. Then the membrane was washed with TBST as above and processed to acquire image by using of ECL (Tanon).

Antibodies. Primary antibodies and dilutions are following: anti-pPH3 antibody (CST, 1:500), anti-Cleaved Caspase3 antibody (CST, 1:500), anti-BrdU antibody (Millipore, 1:20), anti-Ki67 antibody (DAKO, 1:100), anti-GFP antibody (Aves Labs, 1:200), anti-p21 antibody (Santa-cruz, 1:500 for WB), anti-p53 antibody (Novocastra, 1:1000 for WB). Secondary antibodies: anti-rabbit Cy3 (Jackson lab, 1:300), anti-mouse FITC (Vector, 1:300), anti-moues Cy3 (Vector, 1:300), anti-rat Cy3 (Vector, 1:300), anti-chicken Cy5 (Jackson lab, 1:300), Anti-mouse HRP (Jackson lab, 1:3000), anti-rabbit HRP (Jackson lab, 1:3000).

RNA isolation and Real Time PCR. Total RNA was isolated with Trizol (Invitrogen) and was reverse transcribed to cDNA with primescript™ RT reagent kit with gDNA eraser (Takara). Diluted cDNA was then used for Real Time PCR with SYBR Green reagents (Roche) on an ABI Prism Step-One bio-analyzer. Melt curves of specific primers were examined to confirm their specificities and expression data were normalized to *β-actin* mRNA or *18s* rRNA.

Gene	Primer name	Primer sequence
p21	Forward	AGGCAGCGTATATCAGGAG

	Reverse	CCTGACAGATTTCTATCACTCCA
Bax	Forward	AGACAGGGGCCTTTTTGCTAC
	Reverse	AATTCGCCGGAGACACTCG
Noxa	Forward	TCGCAAAAGAGCAGGATGAG
	Reverse	CACTTTGTCTCCAATCCTCCG
LacZ	Forward	AGTTCATTGGGACCATCCTGG
	Reverse	GGGATTCCAATAGCAGCCAT
PCNA	Forward	TTTGAGGCACGCCTGATCC
	Reverse	GGAGACGTGAGACGAGTCCAT
18S RNA	Forward	GTAACCCGTTGAACCCCATT
	Reverse	CCATCCAATCGGTAGTAGCG
β-actin	Forward	CTTCTGACCCATTCCCACCAT
	Reverse	GCTTCTTTGCAGCTCCTTCGT

Tissue culture. MEFs were isolated from E12.5-E14.5 embryos. In brief, embryos were minced well in 1 ml PBS and transferred to 15mL tubes (Corning) with addition of equal volume of 0.25% trypsin. The tubes with minced tissues were kept in 37℃ for 10min with gentle rocking, which is followed by adding 8mL DMEM containing 10% FBS to block the digestion. The digested tissues were pipetted several times and the supernatant was then transferred to 10cm dish for culture in incubator containing 5% CO2. The P0 cells were passaged when reached 80% confluence and named P1. One third of the P1 MEFs were passaged as P2 when reaching confluence while the other 2/3 could be stocked.

Quantification of the clone size. X-gal staining was performed on 10μM thick frozen sections. All pictures were obtained with microscope (Olympus). Pictures with the same magnification and the same resolution were then used to clone size analysis. The relative size of the β-gal positive clones was analyzed with graphic editor software Photoshop. After selecting an interested β-gal positive clone, the Photoshop would tell how much area the clone had in the picture,

which was reflected by the number of pixels this clone possessed in the picture. Then, relative size of the β-gal positive clones was obtained through comparing the pixels each clone occupied in the picture.

Quantification in Western blot. The band in Western blot analysis was quantified with Photoshop software. The β-gal protein level in tissues of each mouse was estimated by comparing the photo density of band representing β-gal protein to that representing input (β-actin) of the tissue.

Blood glucose analysis. Approximately 2 mm tail tip was cut with sharp scissors, and then blood was obtained by direct flow or by gently massaging the tail. Glucometer (Roche) was used to analyze the glucose concentration following the instruction.

Genetic background analysis. Twelve highly polymorphic SNP markers from a panel developed for monitoring mouse stain identity (Petkov PM , Cassell MA , Sargent EE , et al . Development of a SNP genotyping panel for genetic monitoring of the laboratory mouse. Genomics. 2004; 83:902–911) were used to analyze the mouse genetic background. Briefly, DNA fragments were obtained through PCR from the genomic DNA with primers designed for these SNP sites. Desired information about the nucleotide at the SNP site was available after sequencing these DNA fragments.

X-ray irradiation. Whole-body irradiation was employed in this study. Pregnant B6 mice with E12.5 embryos were exposed to 0.2Gy, 0.75Gy and 2.0Gy X-ray irradiation by using Biological X-ray irradiator (RS2000, Rad Source).