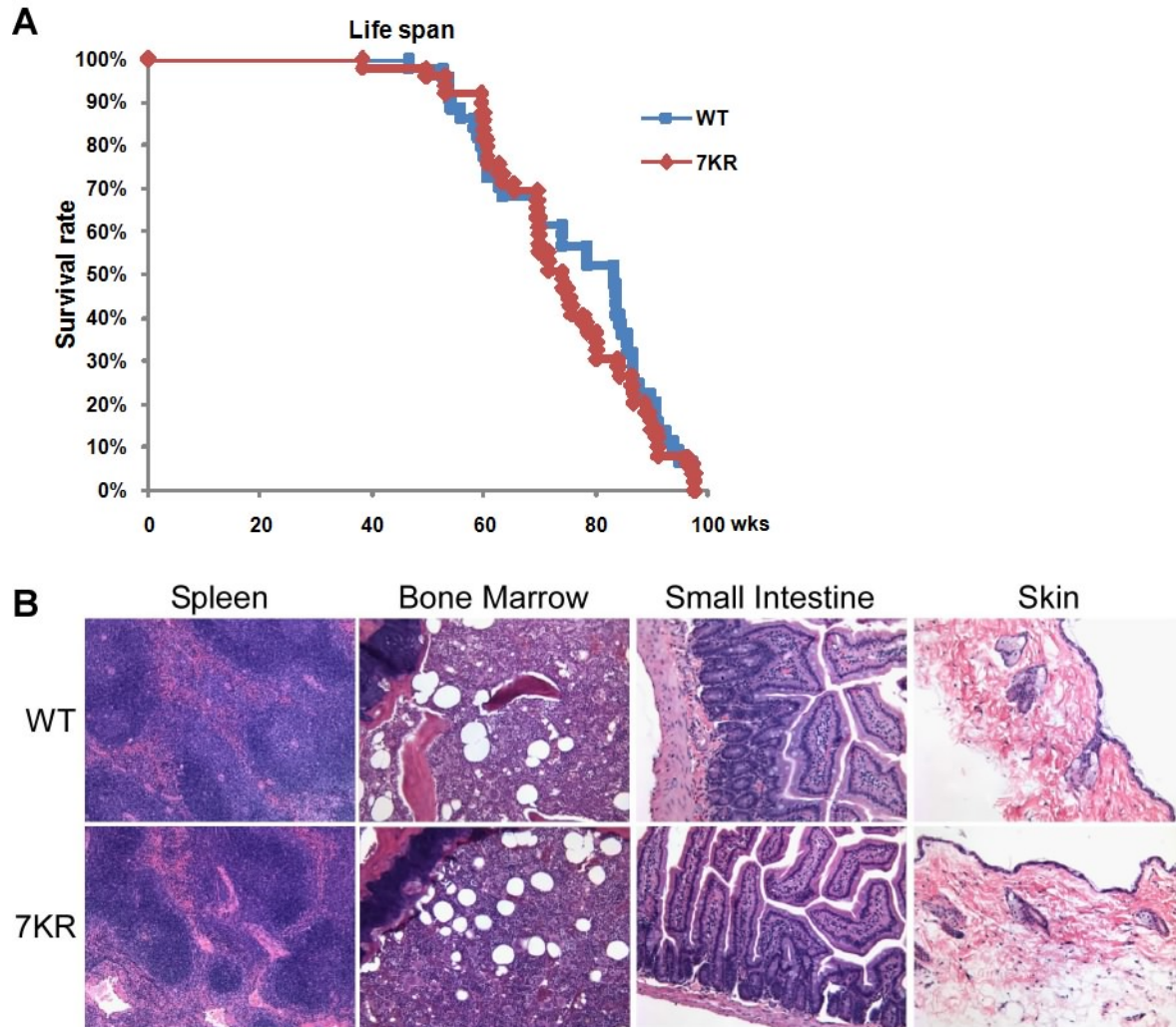
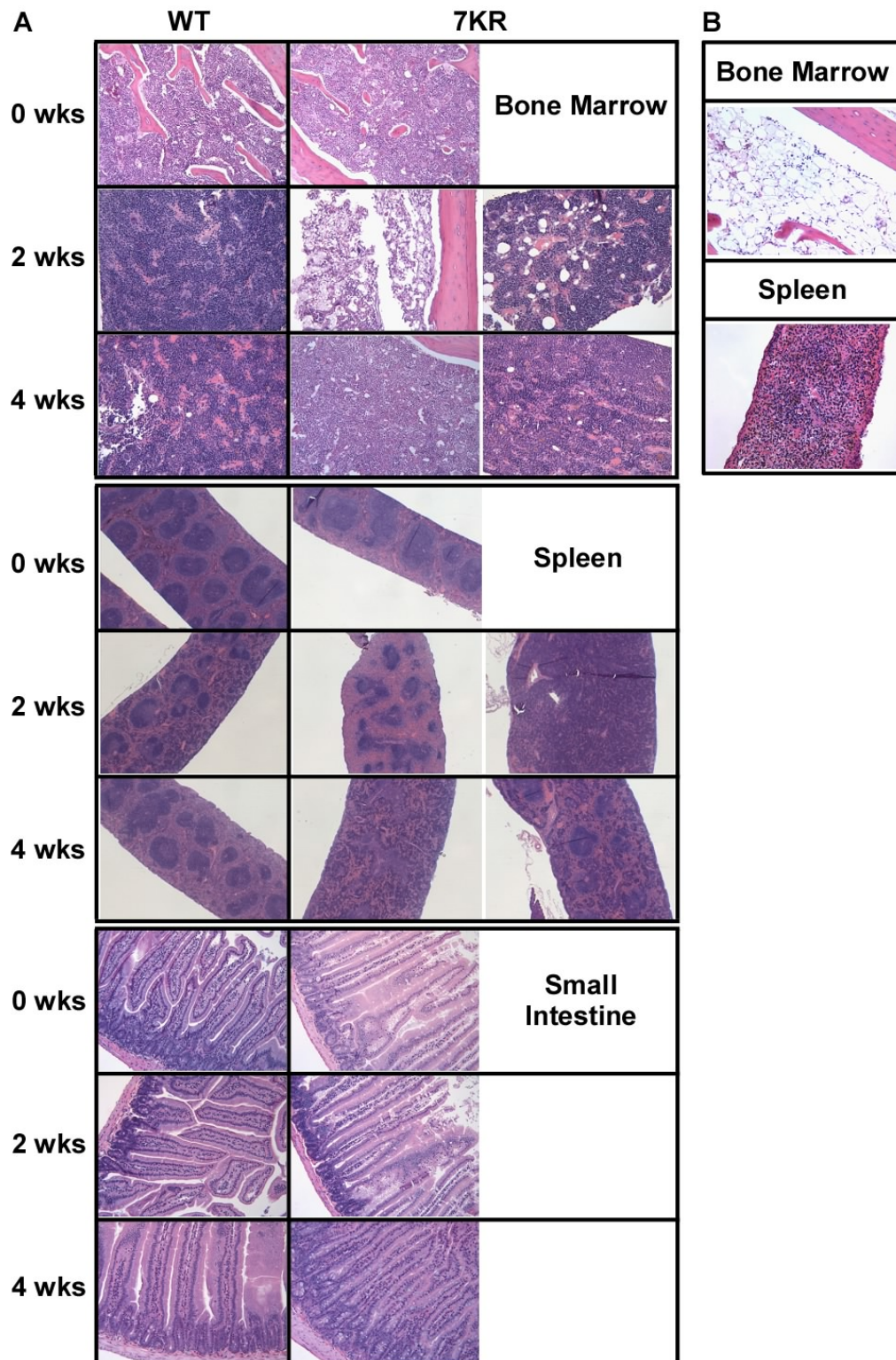


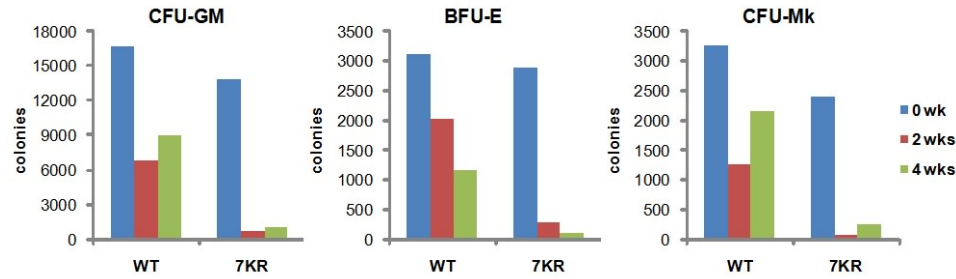
Supplementary Figures



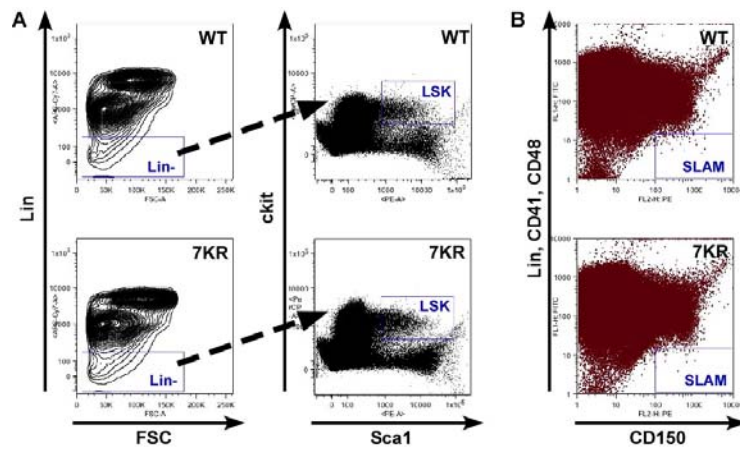
Supplementary Figure 1 Preventing C-terminal modification of p53 has little effect in mouse development. (A) Kaplan-Meier curve of WT (n = 44) and p53^{7KR} (n = 49) mice showing no difference in life span. (B) Histopathology of hematopoietic, intestinal and cutaneous tissues showing no significant differences between one year old WT and p53^{7KR} mice.



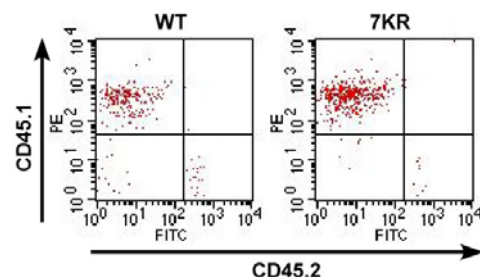
Supplementary Figure 2 Pathological analyses of hematopoietic organs. (A) H&E staining of bone marrows, spleens and small intestines at 2 and 4 weeks after 5Gy of whole body irradiation. (B) Histopathology showing severe atrophy in hematopoietic tissues (spleen and bone marrow) in a p53^{7KR} mouse that died 23 days after 6Gy of whole body irradiation.



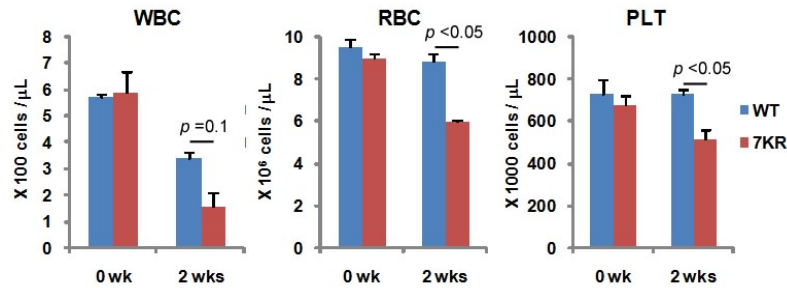
Supplementary Figure 3 Significant reduction of progenitor colony numbers in $p53^{7KR}$ BM isolated 2 and 4 weeks post-irradiation. Mice were exposed to 5Gy of whole body irradiation. BM cells were isolated and pooled from 3 animals 2 and 4 weeks post irradiation and seeded for granulocytic/macrophage (CFU-GM), erythroid (BFU-E) and megakaryocytic (CFU-MK) progenitor cell colony forming assay.



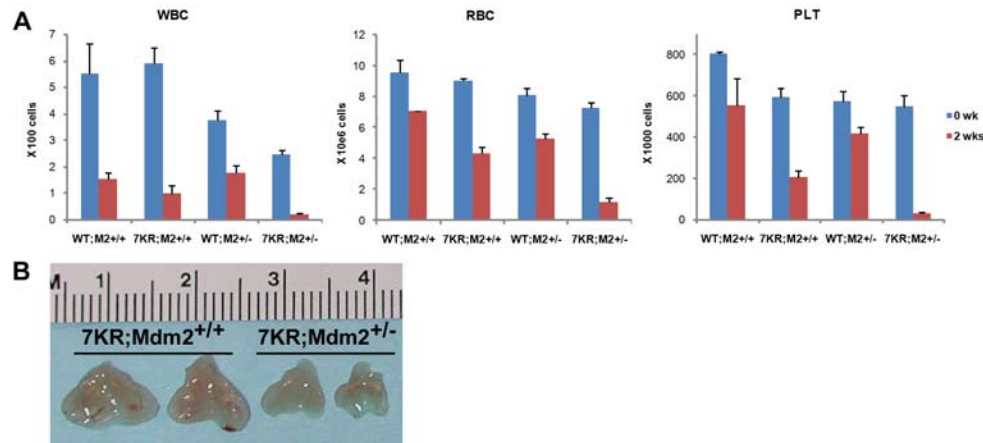
Supplementary Figure 4 FACS analysis of LSK and SLAM enriched HSCs. (A) Bone marrows were isolated from non-irradiated mice and stained with antibodies against hematopoietic lineage (Lin) markers, cell surface marks Sca1 and c-Kit and analyzed by flow cytometry. Lin⁻Sca1⁺c-Kit⁺ sub-population were gated as LSK enriched-HSC cells. (B) Antibody cocktails Lineage markers, CD41, CD48 and CD150 were used for the analysis. Lin⁻CD41⁺CD48⁺CD150⁺ sub-population were gated as SLAM enriched-HSC cells.



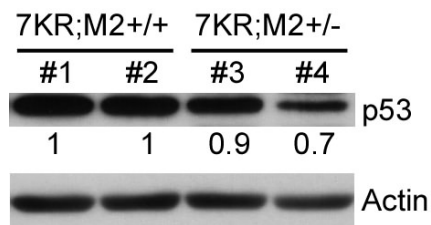
Supplementary Figure 5 FACS analysis of bone marrow transplants. WT and $p53^{7KR}$ mice expressing cell surface marker CD45.2 were exposed to 10Gy of irradiation and transplanted with 1×10^6 of WT bone marrow cells expressing cell surface marker CD45.1. Six weeks post-transplantation, peripheral blood was withdrawn and stained with antibodies against CD45.1 and CD45.2 followed by FACS analysis.



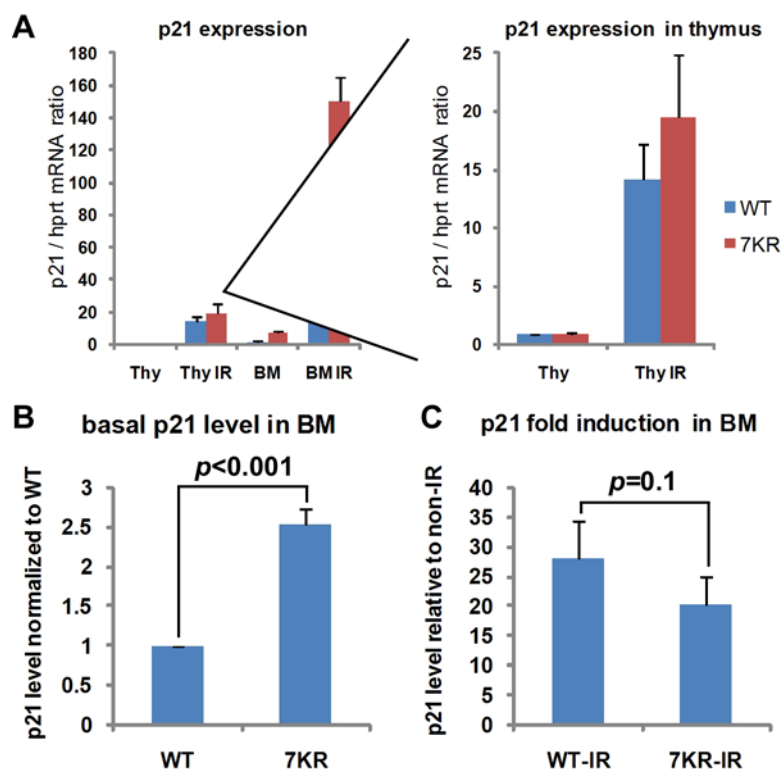
Supplementary Figure 6 CBC analysis of WT and p53^{7KR} mice at 23 weeks old age. CBC analysis showed greater reduction of peripheral blood in 23 weeks old p53^{7KR} mice relative to same age of WT mice 2 weeks post 5Gy irradiation. Error bars represent SEM of 3 animals.



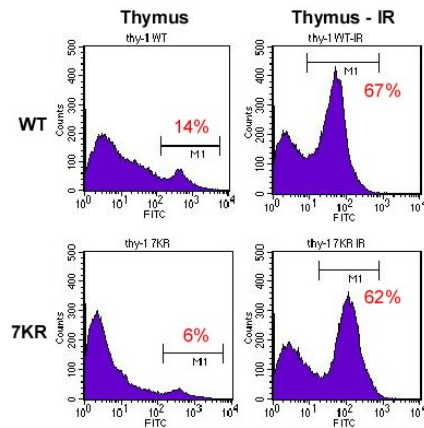
Supplementary Figure 7 p53^{7KR};Mdm2^{+/-} mice have decreased peripheral blood counts and a smaller thymus. (A) CBC analysis of p53^{WT} and p53^{7KR} mice in Mdm2^{+/+} and Mdm2^{-/-} genetic backgrounds. As previously observed in p53^{7KR} mice, CBC analysis showed greater reduction of peripheral blood in p53^{7KR};Mdm2^{+/+} mice 2 weeks after 5Gy irradiation when compared to p53^{WT};Mdm2^{+/+} mice. The most severe pancytopenia was observed in irradiated p53^{7KR};Mdm2^{-/-} mice. Error bars represent SEM of at least 3 animals. (B) Representative thymi from unirradiated p53^{7KR};Mdm2^{+/+} p53^{7KR};Mdm2^{-/-} mice demonstrating substantial size reduction of this organ in p53^{7KR} mice with reduced *Mdm2* gene dosage. This result is similar to that observed previously in mice (Mdm2^{puro/ Δ 7-12}) expressing WT p53 with a hypomorphic *Mdm2* allele (Mendrysa et al, 2003; Mendrysa et al, 2006)..



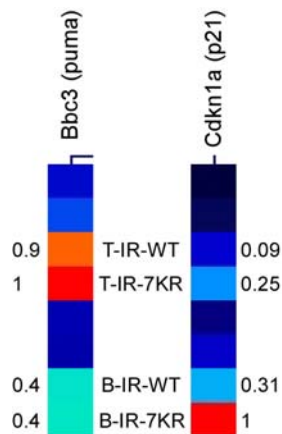
Supplementary Figure 8 Western analysis of p53 abundance. Protein lysate isolated from spleens of 2 p53^{7KR};Mdm2^{+/+} mice (#1, #2) and 2 p53^{7KR};Mdm2^{+/-} littermates (#3, #4) was analyzed. Intensities of p53 signals were normalized to Actin signals and were presented as relative fold differences to the level in sample #1.



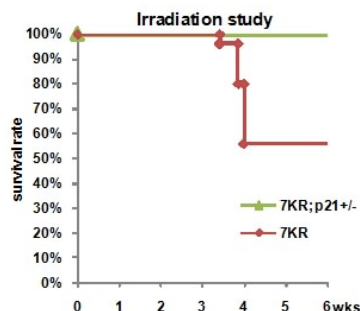
Supplementary Figure 9 Altered p21 expression in p53^{7KR} mice. (A) Thymi from WT and p53^{7KR} mice were isolated 3 hrs after mice were exposed to 5Gy of whole body irradiation for qPCR analysis of p21 expression. Same data are also presented in Figure 6B. (B) p53^{7KR} BM has a higher basal p21 level. RNA was isolated from non-irradiated WT and p53^{7KR} BM. p21 mRNA level was normalized to *hprt* mRNA, then normalized to WT. (C) The fold induction of the p21 gene after irradiation was similar in WT and p53^{7KR} cells. RNA was isolated from non-irradiated and 3hrs post irradiated WT and p53^{7KR} BM. p21 mRNA level from irradiated BM was normalized to non-irradiated BM. Error bars represent the s.d. from at least 4 animals.



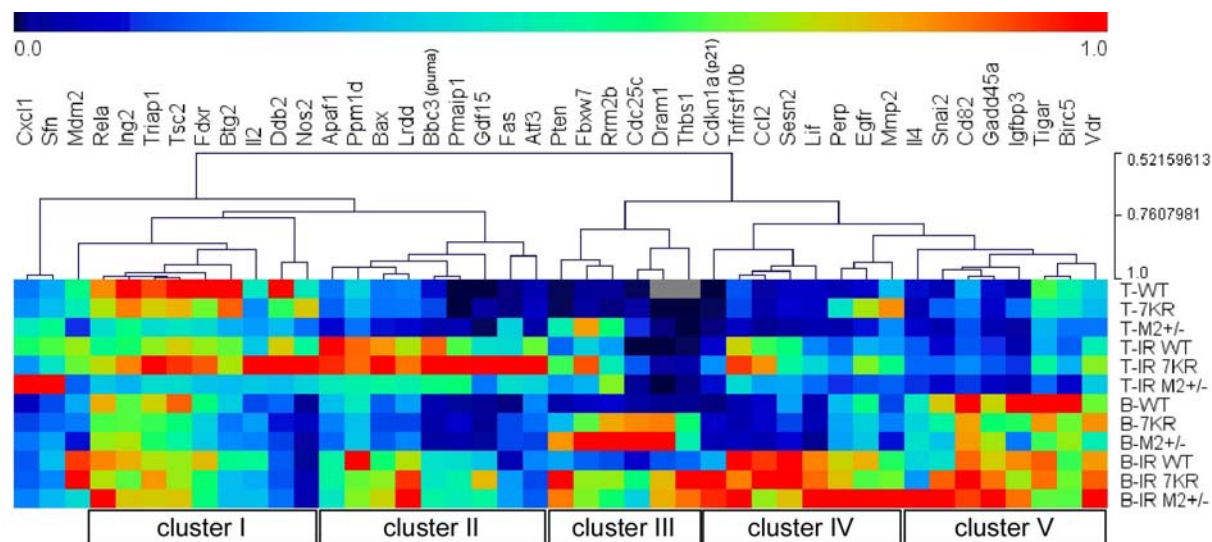
Supplementary Figure 10 Annexin V apoptosis analysis. WT and p53^{7KR} mice were exposed to 5Gy whole body irradiation. Six hours later, thymocytes were isolated from irradiated as well as unirradiated mice and stained with FITC-Annexin V antibodies followed by FACS analysis. Apoptotic cells (FITC positive cells) were quantified.



Supplementary Figure 11 Micro-fluidic chip based qPCR analyses of puma and p21 expression in response to irradiation. Panels containing puma and p21 relative expression were extracted from the cluster analysis shown in Figure 6C. Numbers indicate the expression levels relative to the maximum expression (1) of that gene.

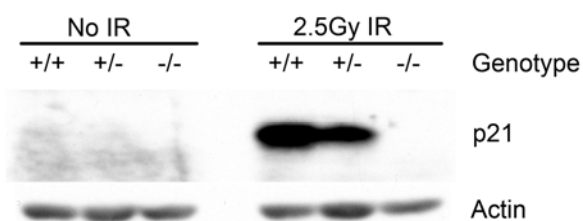


Supplementary Figure 12 The radiosensitivity of p53^{7KR} mice was rescued by losing one allele of p21. None of p53^{7KR};p21^{+/-} mice (n=7) died after being exposed to 5Gy of irradiation. Historic p53^{7KR} data are shown for comparison here.



Supplementary Figure 13 Analyses of gene expression in response to irradiation.

Mice were unirradiated or subjected to 5Gy of irradiation (IR), followed by RNA isolation from thymus (T) or bone marrows (B) 3 hrs post irradiation. Expression of 43 p53 target genes was detected by quantitative RT-PCR using Fluidigm technology. Data were normalized to the average signals of housekeeping genes, *hprt* and *gapdh*, and relative expression of each gene from all samples were scaled from 0 to 1. Hierarchical clustering was performed using MeV 4.4. Cluster I: repressive or less responsive genes. Cluster II: highly IR induced genes in thymus. Cluster III: genes highly affected by p53 activity in BM. Cluster IV: highly IR induced genes in BM. Cluster V: highly expressed genes in BM.



Supplementary Figure 14 p21 expression in response to irradiation. Western analysis of p21 abundance in spleens isolated from p21^{+/+}, p21^{+/-} and p21^{-/-} mice prior to or 8 hours after 2.5Gy of whole body irradiation. Actin is used as a loading control.