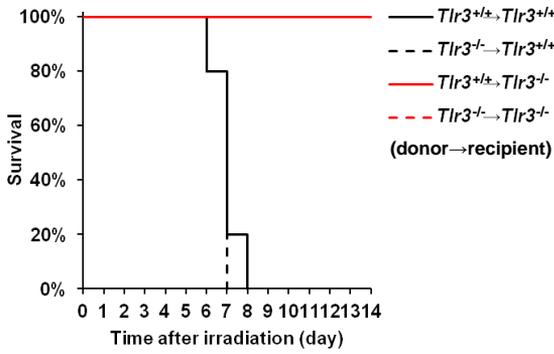
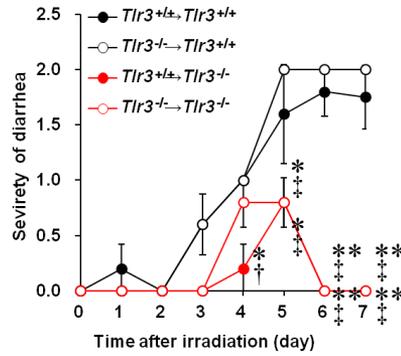
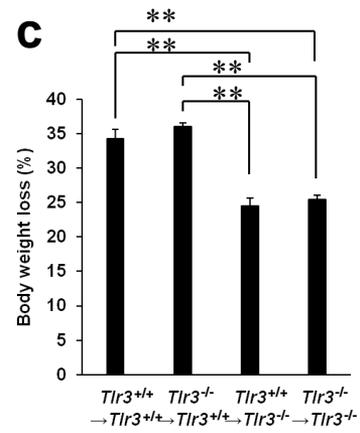
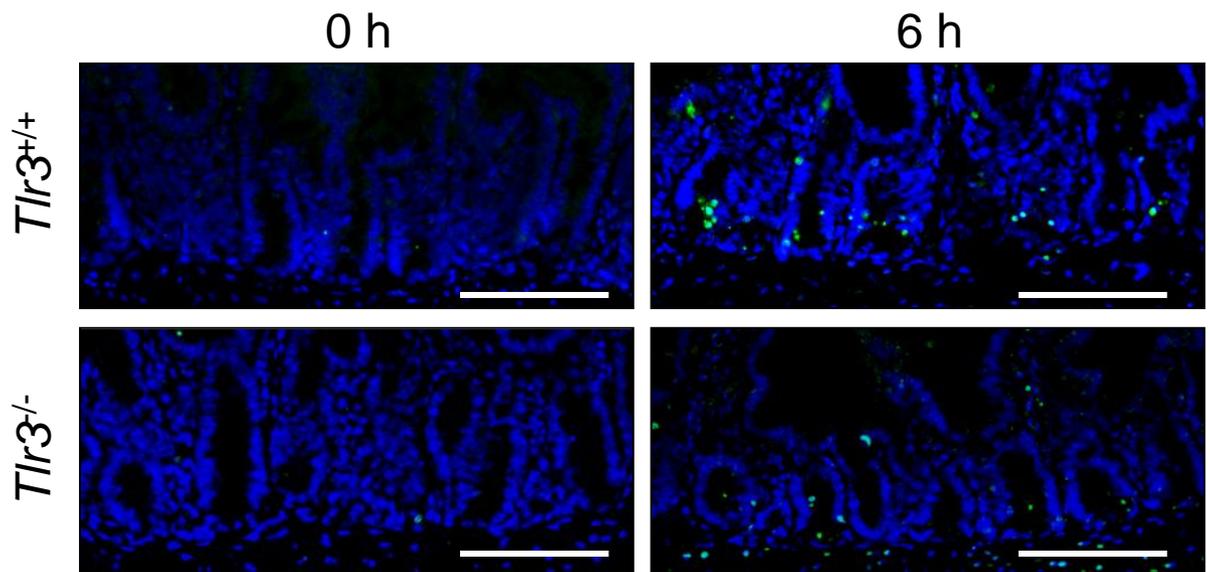


a**b****c**

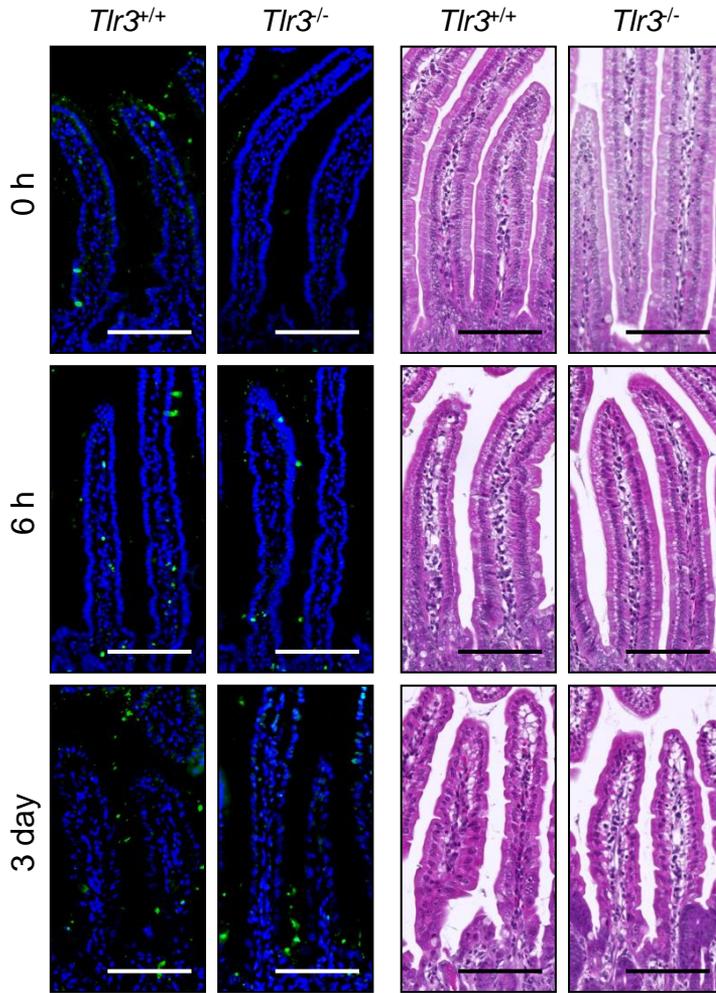
Supplementary Figure 2. Manifestations of radiation-induced GIS of mice received BM cells from $Tlr3^{+/+}$ and $Tlr3^{-/-}$ mice.

$Tlr3^{+/+}$ and $Tlr3^{-/-}$ mice were treated with TBI. Subsequently, mice received a single intravenous injection of BM cells obtained from $Tlr3^{+/+}$ or $Tlr3^{-/-}$ mice. **(a)** Kaplan-Meier survival analyses of $Tlr3^{+/+}$ or $Tlr3^{-/-}$ mice. $n=5$. **(b)** Severity of diarrhea of $Tlr3^{+/+}$ or $Tlr3^{-/-}$ mice. $n=5$. Results are means \pm SEM. *, $P<0.05$. **, $P<0.01$ (vs $Tlr3^{+/+} \rightarrow Tlr3^{+/+}$), †, $P<0.05$, ‡, $P<0.01$ (vs $Tlr3^{-/-} \rightarrow Tlr3^{+/+}$) (unpaired two-tailed Student's t -test) **(c)** Body weight loss of $Tlr3^{+/+}$ or $Tlr3^{-/-}$ mice at day 5. Results are means \pm SEM. $n=5$. *, $P<0.05$. (unpaired two-tailed Student's t -test).



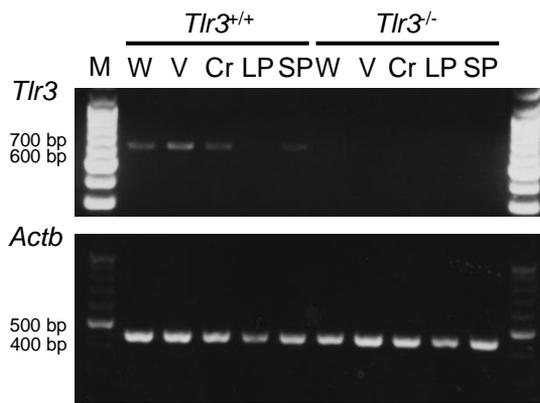
Supplementary Figure 3. Zoomed images of TUNEL-staining of small intestinal crypt after irradiation.

TUNEL-staining of the small intestines of *Tlr3*^{+/+} and *Tlr3*^{-/-} mice 0 and 6 h after 10-Gy TBI. TUNEL-stained epithelium shows green fluorescence. Nuclei were stained with DAPI (blue). Scale bar; 100 μ m.



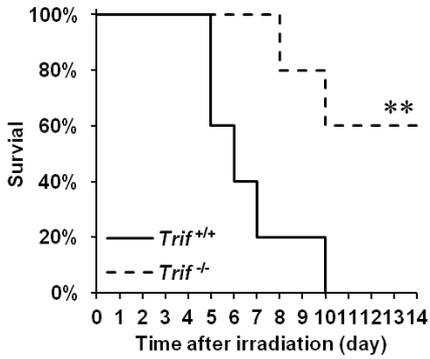
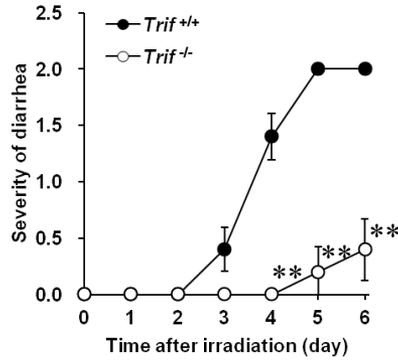
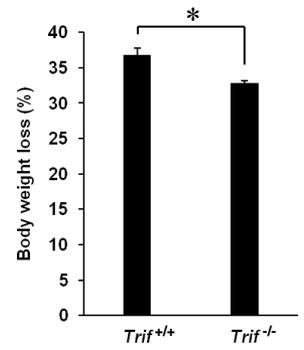
Supplementary Figure 4. Histological observation of small intestinal villi of *Tlr3*^{+/+} and *Tlr3*^{-/-} mice after TBI.

H&E and TUNEL staining of small intestinal villi of *Tlr3*^{+/+} and *Tlr3*^{-/-} mice 0 and 6 h and 3 day. TUNEL-stained epithelium shows green fluorescence. Nuclei were stained with DAPI (blue). Scale bar; 100 μ m.



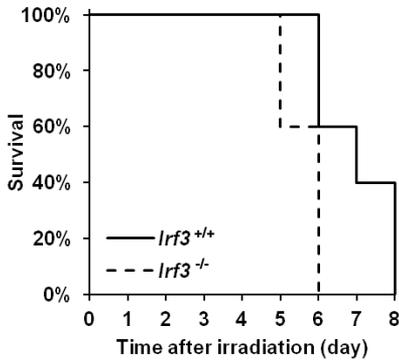
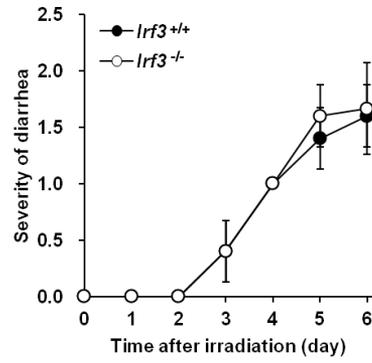
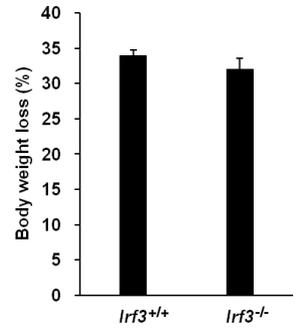
Supplementary Figure 5. Full images of gel electrophoresis.

RT-PCR of *Tlr3* mRNA in the small intestines of *Tlr3*^{+/+} and *Tlr3*^{-/-} mice. M, size marker; W, whole intestine; V, villi; Cr, crypt; LP, lamina propria; SP, spleen.

a**b****c**

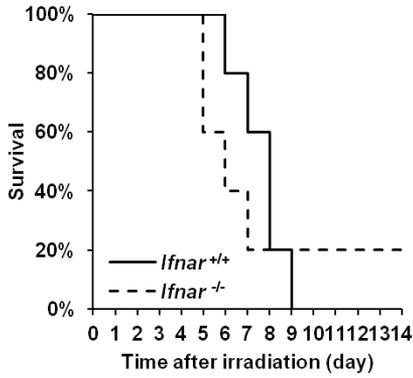
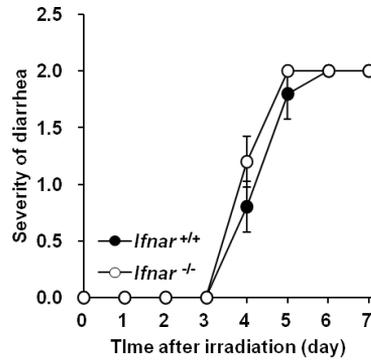
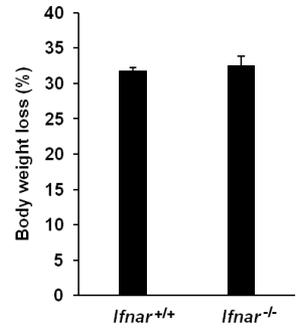
Supplementary Figure 6. Manifestations of radiation-induced GIS of *Trif*^{-/-} mice.

Trif^{+/+} and *Trif*^{-/-} mice were treated with TBI and isologous BMT. (a) Kaplan-Meier survival analyses of *Trif*^{+/+} and *Trif*^{-/-} mice. $n=5$. **, $P<0.01$. (log-rank test) (b) Severity of diarrhea of *Trif*^{+/+} and *Trif*^{-/-} mice. $n=5$. Results are means \pm SEM. **, $P<0.01$. (unpaired two-tailed Student's t -test) (c) Body weight loss of *Trif*^{+/+} and *Trif*^{-/-} mice at day 5. Results are means \pm SEM. $n=5$. *, $P<0.05$. (unpaired two-tailed Student's t -test).

a**b****c**

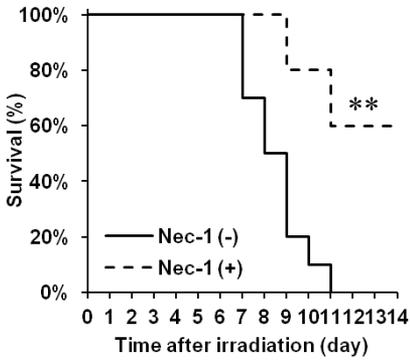
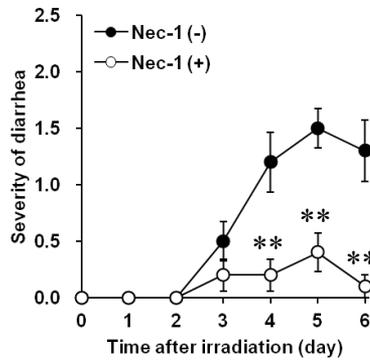
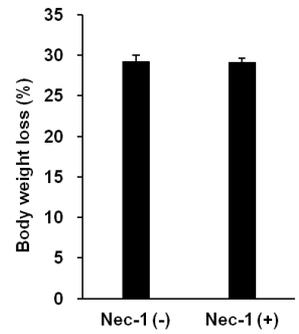
Supplementary Figure 7. Manifestations of radiation-induced GIS of *Irf3*^{-/-} mice.

Irf3^{+/+} and *Irf3*^{-/-} mice were treated with TBI and isologous BMT. **(a)** Kaplan-Meier survival analyses of *Irf3*^{+/+} and *Irf3*^{-/-} mice. *n*=5. **(b)** Severity of diarrhea of *Irf3*^{+/+} and *Irf3*^{-/-} mice. *n*=5. Results are means \pm SEM. **(c)** Body weight loss of *Irf3*^{+/+} and *Irf3*^{-/-} mice at day 5. *n*=5. Results are means \pm SEM.

a**b****c**

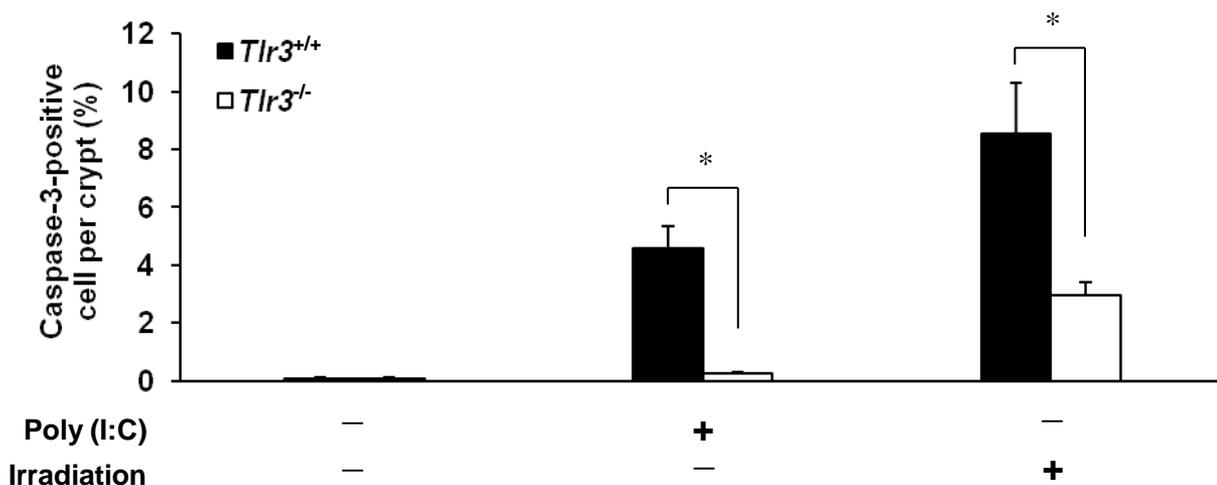
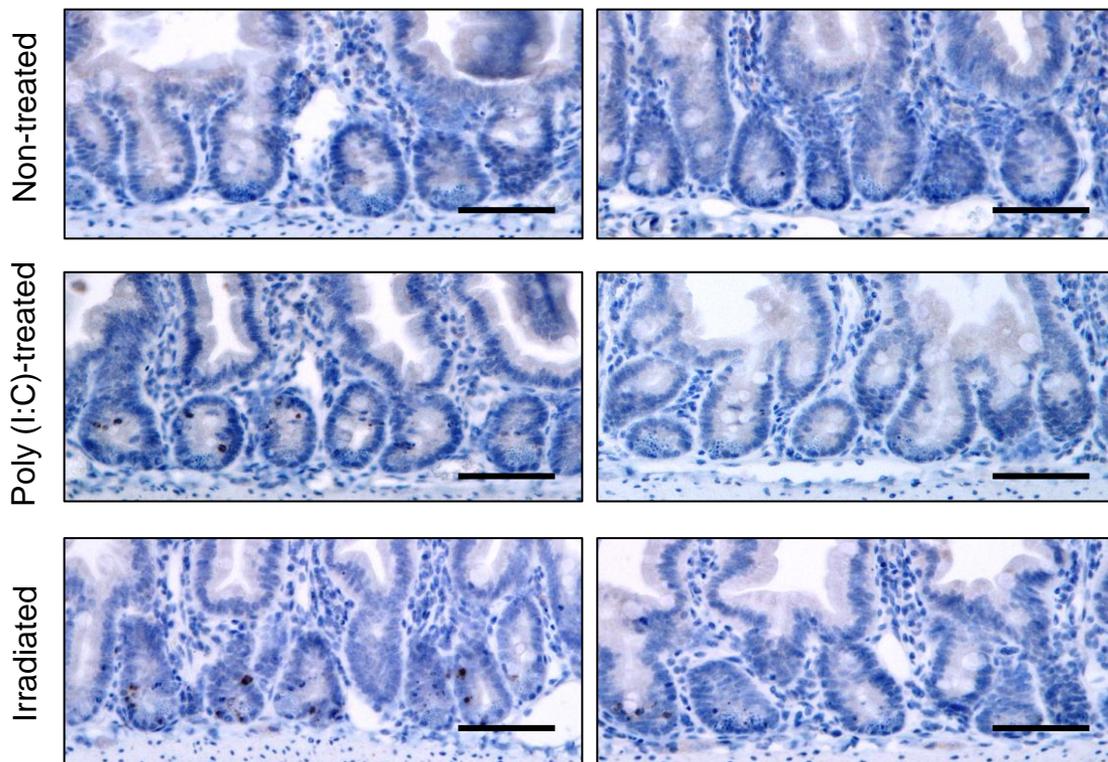
Supplementary Figure 8. Manifestations of radiation-induced GIS of *Ifnar*^{-/-} mice.

Ifnar^{+/+} and *Ifnar*^{-/-} mice were treated with TBI and isologous BMT. **(a)** Kaplan-Meier survival analyses of *Ifnar*^{+/+} and *Ifnar*^{-/-} mice. $n=5$. **(b)** Severity of diarrhea of *Ifnar*^{+/+} and *Ifnar*^{-/-} mice. $n=5$. Results are means \pm SEM. **(c)** Body weight loss of *Ifnar*^{+/+} and *Ifnar*^{-/-} mice at day 5. $n=5$. Results are means \pm SEM.

a**b****c**

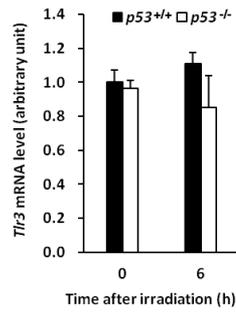
Supplementary Figure 9. Manifestations of radiation-induced GIS of Nec-1-treated mice.

Nec-1-treated mice were treated with TBI and isologous BMT. **(a)** Kaplan-Meier survival analyses of non-treated and Nec-1-treated mice after TBI and isologous BMT. $n=10$. **, $P<0.01$. (log-rank test) **(b)** Severity of diarrhea of non-treated and Nec-1-treated mice. $n=10$. Results are means \pm SEM. **, $P<0.01$. (unpaired two-tailed Student's t -test) **(c)** Body weight loss of non-treated and Nec-1-treated mice at day 5. $n=10$. Results are means \pm SEM.

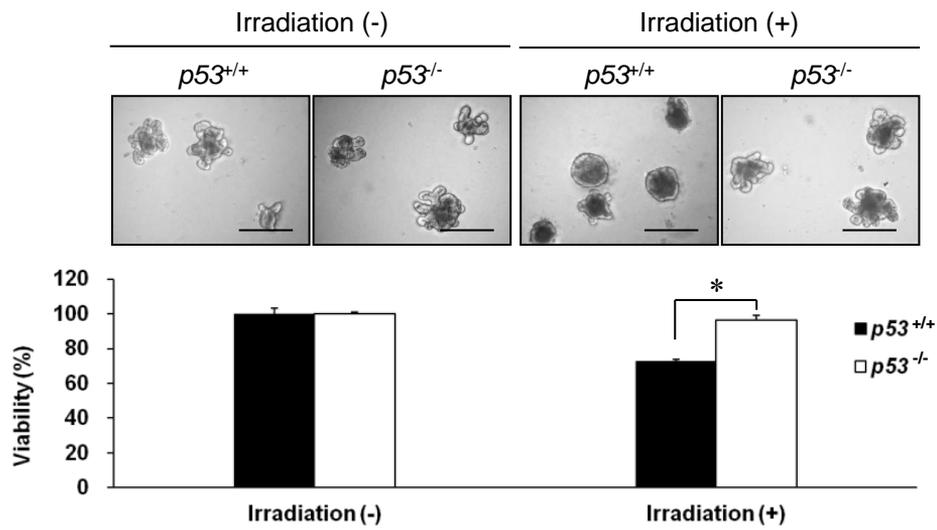
Tlr3^{+/+}*Tlr3*^{-/-}

Supplementary Figure 10. TLR3-dependent crypt cell death is mediated by caspase-3

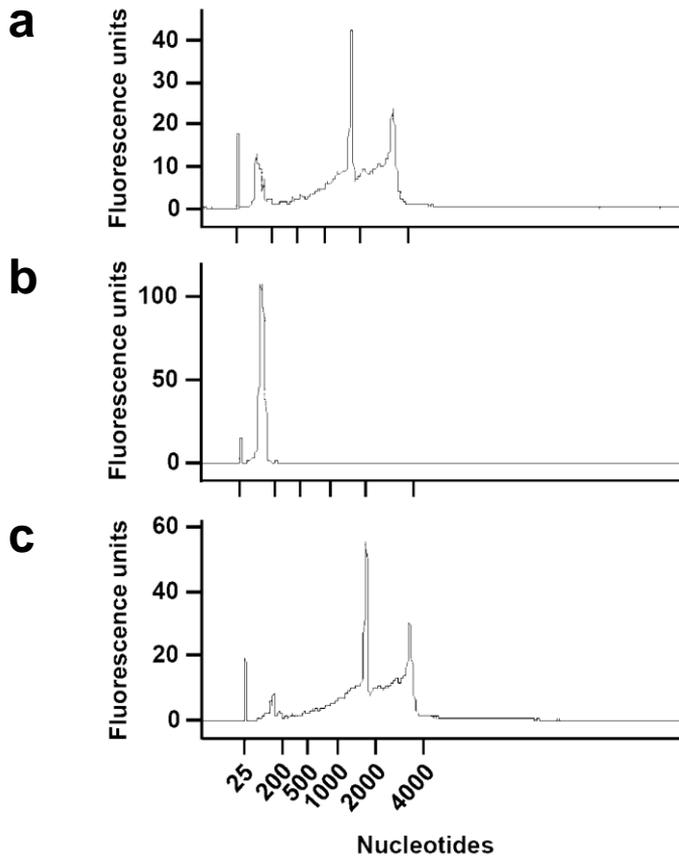
Immunohistochemical detection of active caspase-3 in the small intestinal crypts of *Tlr3*^{+/+} and *Tlr3*^{-/-} mice 6 h after TBI or intraperitoneal injection of poly I:C. Active caspase-3-positive cells are stained in brown. Scale bar; 100 μ m. Lower panel shows numbers of active caspase-3-positive cells. $n=3$. Results are means \pm SEM. *, $P < 0.05$. (unpaired two-tailed Student's t -test).



Supplementary Figure 11. *Tlr3* mRNA expression in crypt cells of *p53*^{+/+} and *p53*^{-/-} mice. Quantitative real-time PCR of *Tlr3* mRNA expression in crypt cells of *p53*^{+/+} and *p53*^{-/-} mice. *n*=3. Results are means \pm SEM.

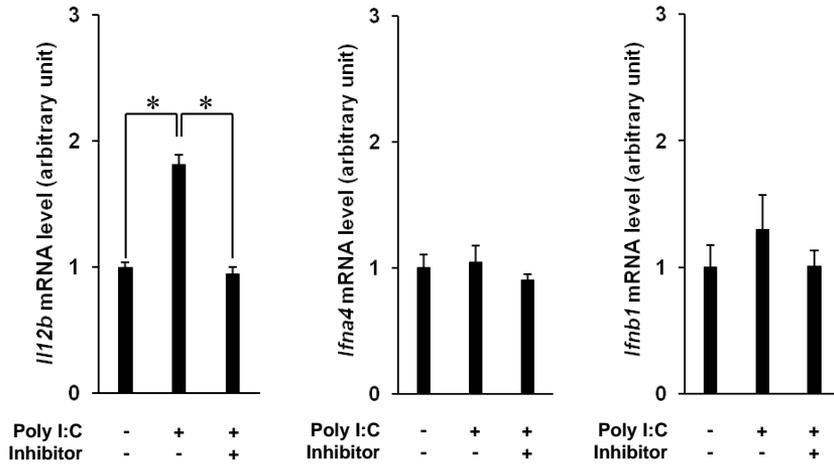


Supplementary Figure 12. Radiation induces p53-dependent cell death in crypt-villus organoid. Representative images of crypt-villus organoids of *p53*^{+/+} and *p53*^{-/-} mice on day 1 after irradiation. Scale bar; 200 μ m. Lower panel shows the viability. Viability was measured in triplicate. Results are means \pm SEM. *, $P < 0.05$ (unpaired two-tailed Student's *t*-test)



Supplementary Figure 13. Confirmation of the sizes of small and large RNA prepared from irradiated small intestine.

Bioanalyzer graphical data of the size distribution of (a) total RNA, (b) small RNA, and (c) large RNA prepared from irradiated small intestine. The peak at 25-nt is an internal standard.



Supplementary Figure 14. Effects of TLR3/dsRNA complex inhibitor on poly I:C-induced expressions of cytokine mRNA of CD8 α^+ splenic dendritic cells.

CD8 α^+ splenic dendritic cells were pretreated with TLR3/dsRNA complex inhibitor for 1 h before stimulation with poly I:C. After 12 h of incubation, expression levels of mRNA encoding IL-12p40, IFN- α 4, and IFN- β were measured in triplicate. Results are means \pm SEM. *, $P < 0.05$ (unpaired two-tailed Student's t -test)