**Supplementary Figure 1.** Casp8 suppresses programmed necrosis. (a) Viability (left) and RIP3, RIP1, Casp8, and β-actin immunoblot (right) of L929 cells expressing a control scramble shRNA or RIP3-specific shRNA following transfection with non-targeting (NT) or Casp8-specific siRNA. Cell viability was determined 96 h post-transfection by measuring intracellular ATP levels (Cell Titer-Glo Luminescent Cell Viability Assay kit, Promega). (b) Viability (left) and M45 immunoblot (right) of L929 cells transduced with empty vector (EV), M45-myc, or M45mutRHIM-myc at 96 h post-transfection with NT or Casp8 siRNA. (c) Viability of L929 cells expressing a control scramble shRNA or RIP3-specific shRNA following treatment for 18 h with zVAD-fmk (25 μM) in the absence or presence of the RIP1 kinase inhibitor Nec-1 (30 μM). (d) Viability of L929 cells transduced with empty vector (EV), M45-myc, or M45mutRHIM-myc following treatment as described in c. (e) Percent cell death, calculated as the difference between the indicated treatment and the EV-transfected cell viability, in L929 cells expressing an EV or M45-myc (left), or control scramble shRNA or RIP3-specific shRNA (right), constructs at 96 h post-transfection with plasmid encoding M36 and cultured in the presence of Nec-1 (30μM) or vehicle DMSO for 12 h. (f) L929 cells carrying a control scramble shRNA or RIP3-specific shRNA following cotransfection with M36 or EV control plasmids together with a GFP expression plasmid. The percent GFP positive cells was calculated by comparing to control EV-transfected cells determined by flow cytometry at 48 h post-transfection.
**Supplementary Figure 2.** Embryonic lethality and RIP3 detection in Casp8-deficient mice. (a) Photomicrographs of E11.5 yolk sac and embryo with the indicated genotype, highlighting the region of hyperemia (arrow in right panel). (b) PECAM (red), RIP3 (green) and DAPI (blue) fluorescent staining of representative Casp8+/Rip3+/- and Casp8−/−Rip3+/- E10.5 yolk sacs (400X original magnification). (c) RIP3 (red), CD41 (green) and DAPI (blue) fluorescent staining of representative Casp8+/−Rip3+/- yolk sacs (630X original magnification). (d) PECAM-1 (CD31) staining of a whole-mount E9.5 and E11.5 yolk sac from a representative Casp8−/−Rip3+/- (left panels) and Casp8+/−Rip3+/- (right panels) embryo (200X).
**Supplementary Figure 3.** *Casp8⁻∕⁻Rip3⁻∕⁻* mice are viable. (**a**) PCR confirmation of genotype on tail DNA from the indicated *Casp8⁺∕⁺Rip3⁺∕⁺* intercross progeny to detect wild-type (upper bands) and mutant (lower bands) *Casp8* and *Rip3* alleles. (**b**) Photograph of 4-month-old *Casp8⁺⁻Rip3⁻⁻* mouse bred from a DKO cross along side a *Casp8⁻⁻Rip3⁻⁻* mice bred from an intercross.
Supplementary Figure 4. Susceptibility to LPS+GalN induced hepatitis in Casp8<sup>+/+</sup>Rip3<sup>+/+</sup>, Casp8<sup>+/+</sup>Rip3<sup>−/−</sup>, Casp8<sup>−/−</sup>Rip3<sup>+/+</sup> and control TRIF-deficient (lps2/lps2) mice. (a) Kaplan-Meier survival plot of indicated strains of mice following intraperitoneal inoculation with LPS (100 ng) and GalN (20 mg). (b) Histology of liver sections from indicated strains of mice 8h following injection with LPS/GalN.
Supplementary Figure 5. DKO mice accumulate aberrant T-cells. (a) Photographs of six-month-old Casp8+/+Rip3+/+ and Casp8−/−Rip3−/− mice. The arrow indicates enlarged cervical LN present in the DKO mouse. (b) Images of spleen and axial LNs from Casp8+/+Rip3+/+ and Casp8+/−Rip3−/− mice of the indicated ages. (c) Graph of weights of spleen from mice of the indicated genotype. (d) The numbers of cells and (e) numbers of B and T cells recovered from spleens from mice with the indicated genotype. Samples were analyzed using Student’s t-test. (f) CD4 vs. CD8 expression of CD3+ T cells in spleen (top panels), LN (middle panels) and thymus (bottom panels) identified as in C, in representative wild-type (left panels), Casp8+/−RIP3+/− (middle panels) and Casp8+/−RIP3−/− (right panels) mice. (g) Frequency (graph) and level of CD3+CD4−CD8−B220+ T cells from LN of mice.