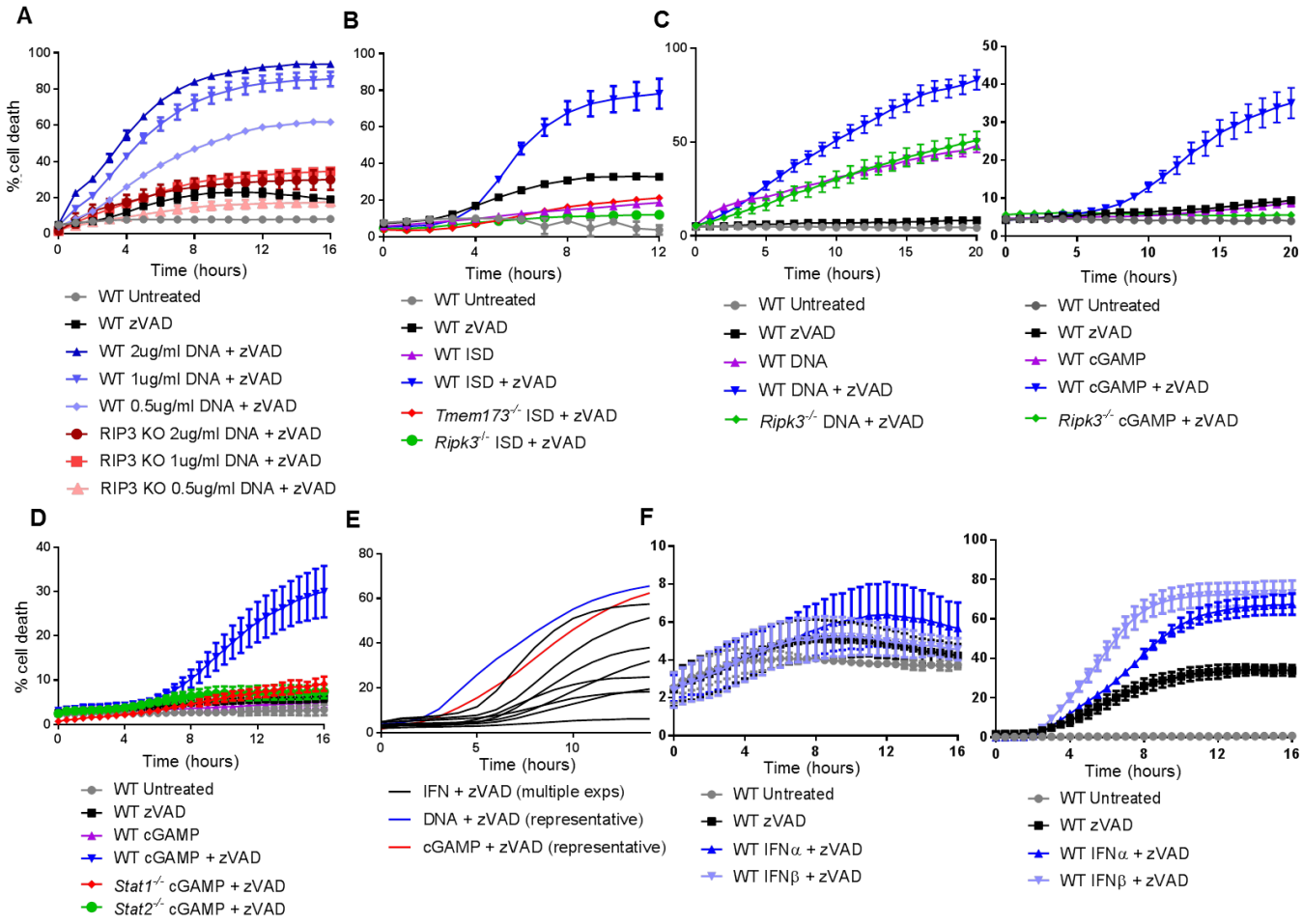


**Figure S1: DNA-ligand driven cell death and IFN signaling** (A) Kinetic cell death of WT or *Ripk3*$^{-/-}$ BMDM after treatment with various doses of cytosolic DNA + 50 μM zVAD. (B) Kinetic cell death of WT, *Tmem173*$^{-/-}$, or *Ripk3*$^{-/-}$ BMDM following treatment of 2 μg/ml interferon stimulatory DNA (ISD) and 50 μM zVAD. (C) Kinetic cell death of WT or *Ripk3*$^{-/-}$ MEFs after treatment with 2 μg/ml cytosolic DNA or 2 μg/ml cGAMP and 50 μM zVAD. (D) Kinetic cell death of WT, *Stat1*$^{-/-}$, or *Stat2*$^{-/-}$ BMDM after treatment with 2 μg/ml cGAMP and 25 μM pan-caspase inhibitor zVAD. (E) Kinetic cell death of WT BMDM following treatment with 100 units/ml IFN and 25 μM zVAD, 2 μg/ml cytosolic DNA and 50 μM zVAD, or 2 μg/ml cGAMP and 25 μM zVAD. Black lines are individual experiments, representative of the variability observed upon stimulus with recombinant IFN. Blue line and red line are one experiment of the representative average of response. (F) Kinetic cell death of WT BMDM treated with 100 units/ml of IFNα or IFNβ and 50 uM zVAD. Two independent experiments with two biological replicates in each experiment are shown to show variability in response magnitude.

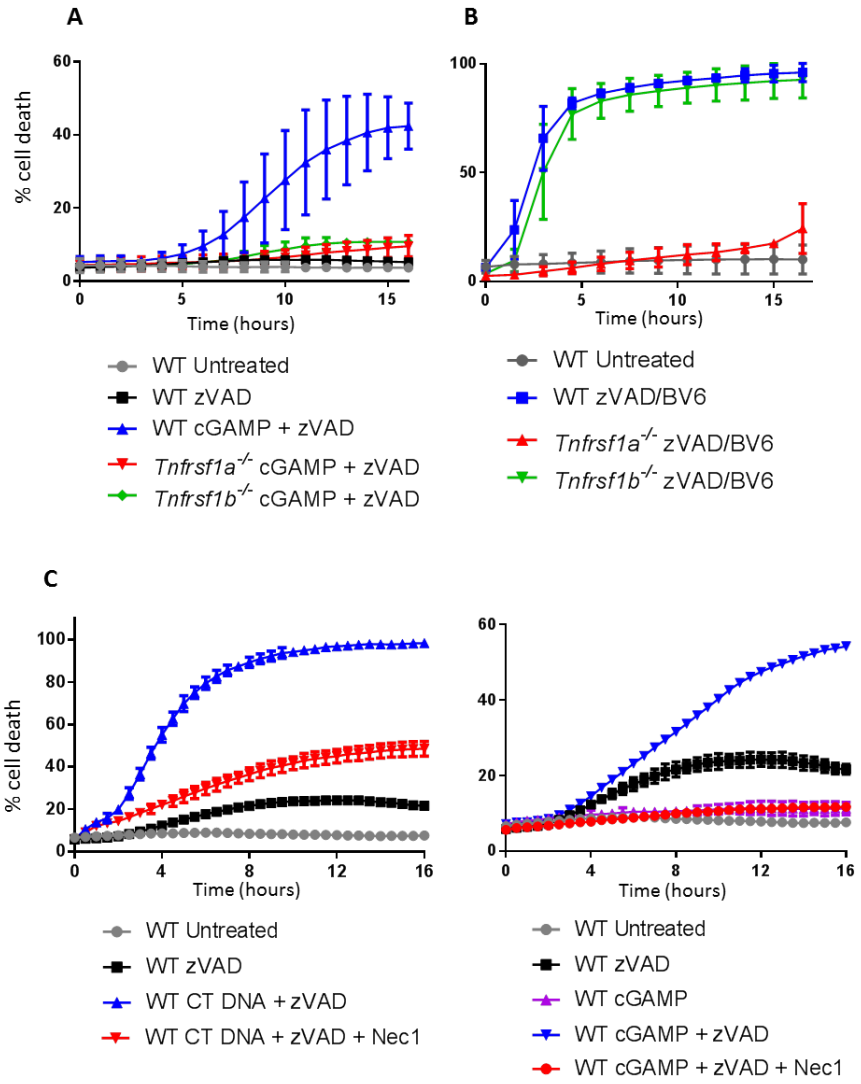


**Figure S2: Roles of TNFR1 and TNFR2 in necroptosis** (A) Kinetic cell death of WT, *Tnfrsf1a*$^{-/-}$, or *Tnfrsf1b*$^{-/-}$ BMDM after treatment with 2 µg/ml cGAMP and 25 µM pan-caspase inhibitor zVAD. (B) Kinetic cell death of WT, *Tnfrsf1a*$^{-/-}$, or *Tnfrsf1b*$^{-/-}$ BMDM after treatment with 1 µM cIAP antagonist BV6 and 25 µM pan-caspase inhibitor zVAD. (C) Kinetic cell death of WT cells treated with 2 µg/ml cytosolic DNA and 50 µM zVAD, or 2 µg/ml cGAMP and 25 µM zVAD, with or without Necrostatin-1.

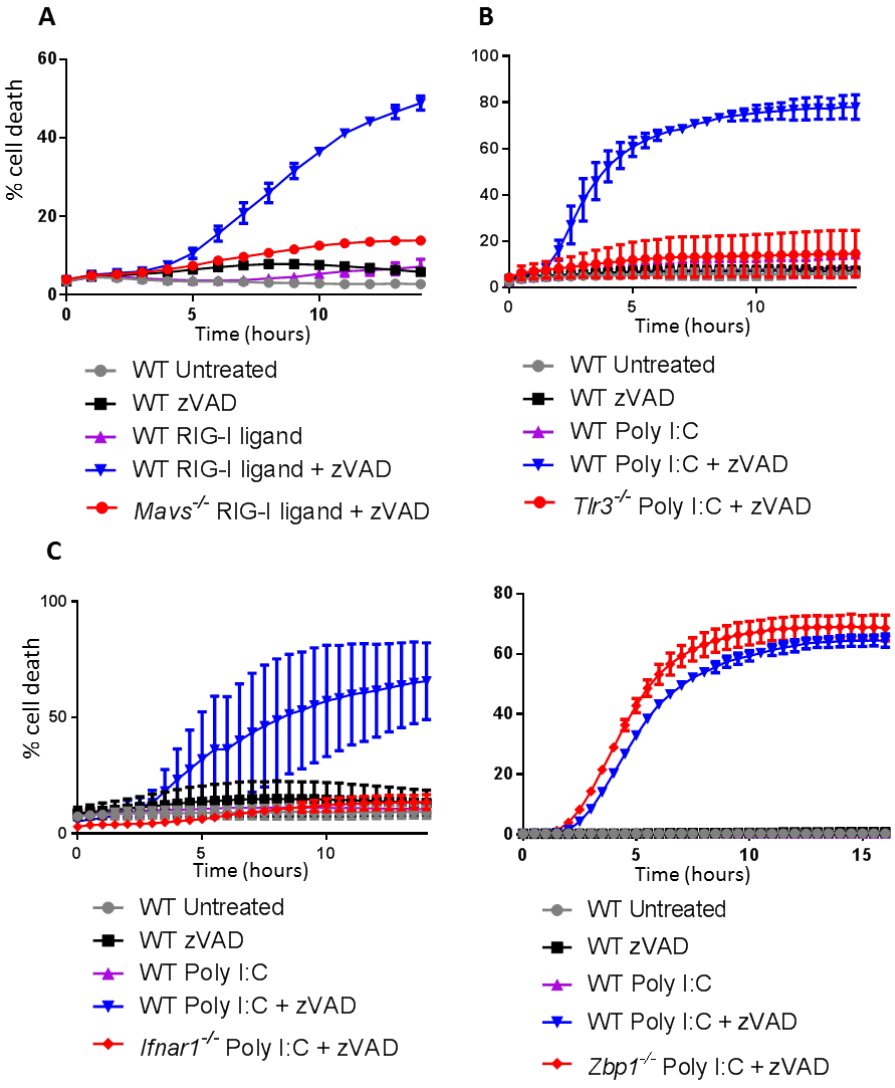


**Figure S3: Pathways stimulated by 5' triphosphate RNA (RIG-I ligand) or Poly(I:C)** (A) Kinetic cell death of WT or *Mavs*$^{-/-}$ BMDM after treatment with 1 μg/ml tri-phosphate RNA (RIG-I ligand) and 25 μM pan-caspase inhibitor zVAD. (B) Kinetic cell death of WT or *Tlr3*$^{-/-}$ BMDM after treatment with 1 μg/ml poly(I:C) and 25 μM zVAD. (C) Kinetic cell death of WT or *Ifnar1*$^{-/-}$ BMDM after treatment with 1 μg/ml poly(I:C) and 25 μM zVAD. (D) Kinetic cell death of WT or *Zbp1*$^{-/-}$ BMDM after treatment with 1 μg/ml poly (I:C) and 25 μM zVAD.

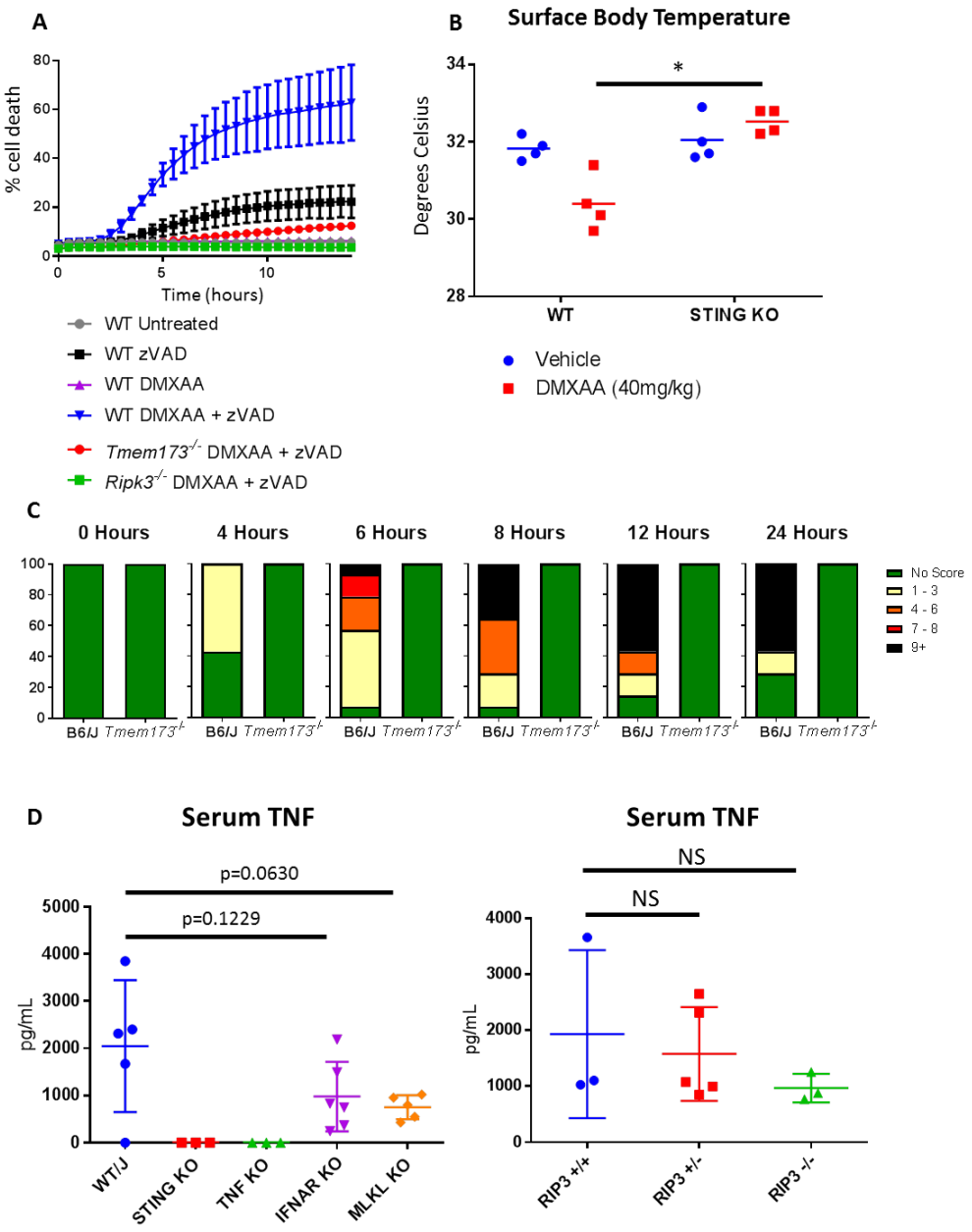


**Figure S4: The effects of STING agonist DMXAA *in vitro* and *in vivo*** (A) Kinetic cell death of WT, *Tmem173*$^{-/-}$, or *Ripk3*$^{-/-}$ BMDM after treatment with 30 μg/ml DMXAA and 25 μM pan-caspase inhibitor zVAD. (B) Surface body temperature of WT or *Tmem173*$^{-/-}$ mice following IP injection of 40 mg/kg DMXAA. Temperatures are an average of three readings taken 8 hours post treatment. (C) Clinical scores of WT or *Tmem173*$^{-/-}$ mice following IP injection of 40 mg/kg DMXAA. Scores were cumulative based on signs as listed in Methods. (D) Serum TNF measured by ELISA of WT, *Tmem173*$^{-/-}$, *Tnf*$^{-/-}$, *Ifnar1*$^{-/-}$, *Mlkl*$^{-/-}$, or *Ripk3* littermates following IP injection of 40 mg/kg DMXAA. Serum was collected 6 hours post injection.