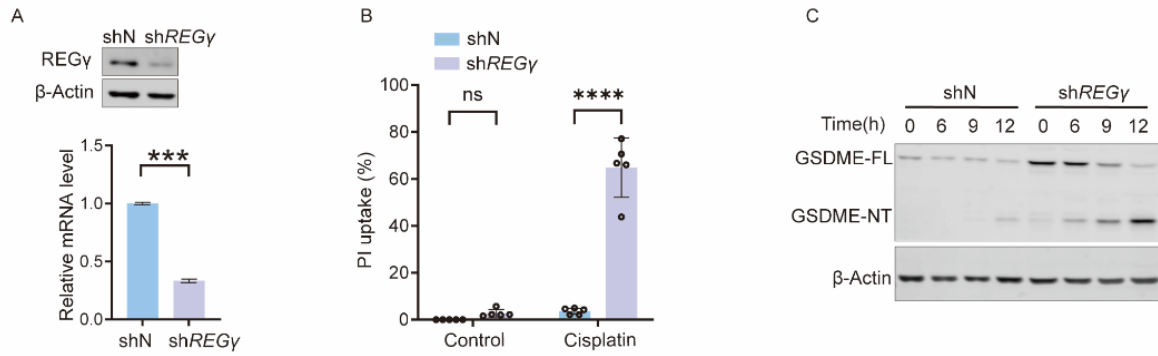
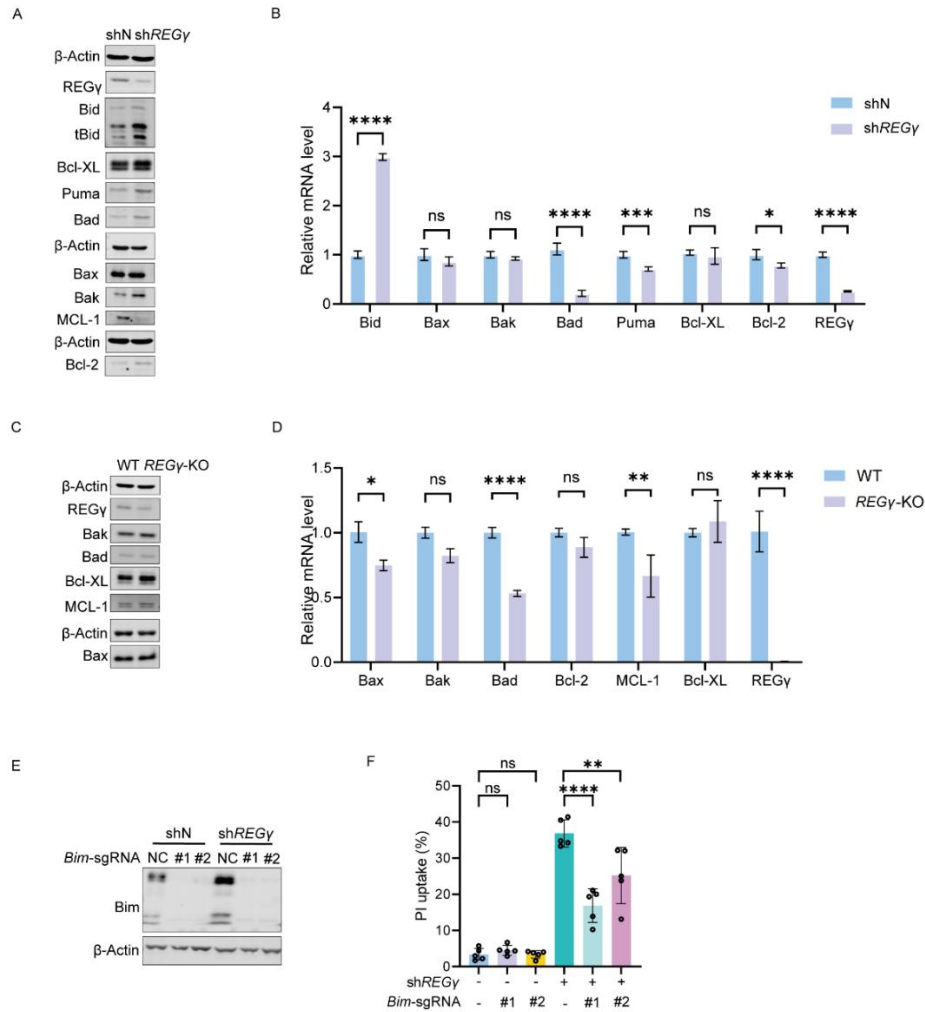
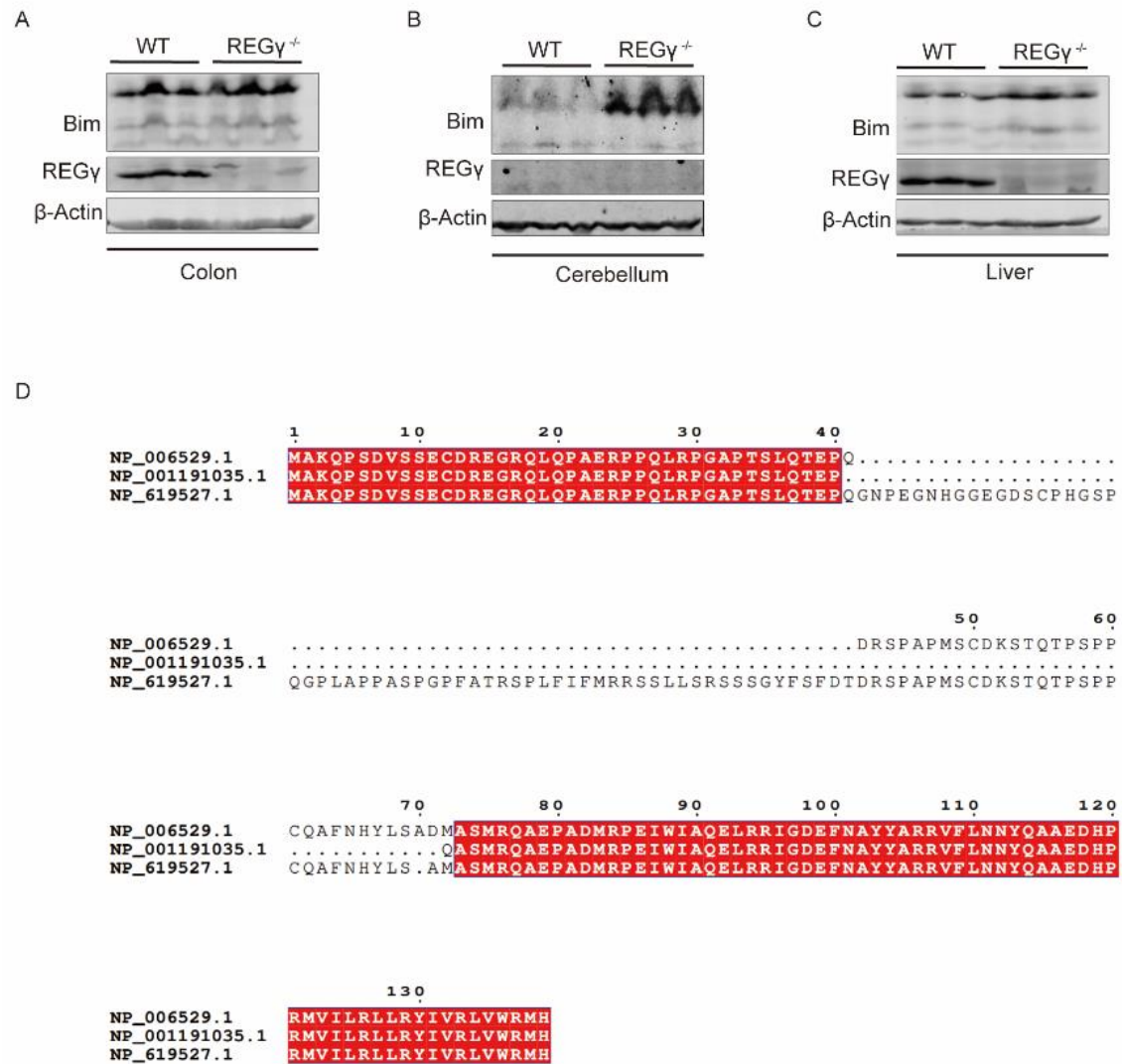




Supplementary Figure 1. REGγ deficiency promoted pyroptotic cell death. (A) Protein level and mRNA level in HeLa shN and HeLa shREGγ. Differences were measured by T test. (B) Quantitated results in Fig. 1A. Five fields were selected to count the cells with Hoechst 33342/PI double staining. (C) HeLa cells were treated with 40 μM cisplatin at different time and then analyzed for the expression of GSDME by western blot. FL: full length, NT: N-terminus. Data are means ± SD taken from three technical replicates. ns, not significant, *P < 0.05, **P < 0.01, ***P < 0.001. Differences were measured by T test and two-way ANOVA.

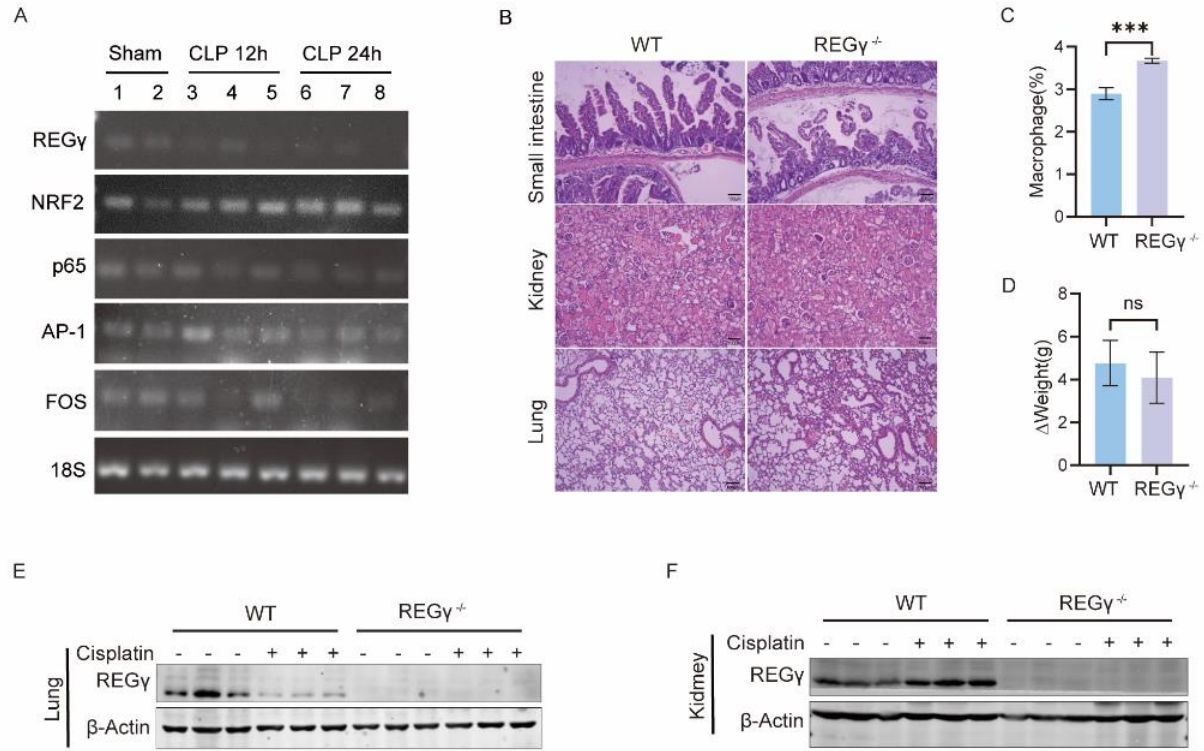


Supplementary Figure 2. Loss of Bim alleviated the promotive effect of REG γ deficiency on pyroptosis. (A) The protein levels of BCL-2 family members in HeLa cells. (B) The mRNA levels of BCL-2 family members in HeLa cells. (C) The protein levels of BCL-2 family members in BMDMs. (D) The mRNA levels of BCL-2 family members in BMDMs. (E) HeLa *Bim*-knockout cells and HeLa *Bim*-knockout-shREG γ cells were constructed. Cells were analyzed by western blot. NC means cells were transfected with sgRNA negative control. #1/2 means two different *Bim*-specific sgRNAs. (F) Quantitated results of Hoechst 33342/PI staining in Fig. 2F. Differences were measured by two-way ANOVA. ns, not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

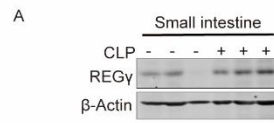


Supplementary Figure 3. REGγ mediated ubiquitin-ATP-independent degradation of Bim.

(A-C) Colon, cerebellum and liver from WT mice and *REGγ*^{-/-} mice were assessed for Bim expression by western blot, respectively. (D) Sequence alignment of BimEL (down), BimL (up) and BimS (medium).



Supplementary Figure 4. Cisplatin injection downregulated the expression of REGγ in the lung tissue. (A) The expression level of transcription factors regulating REGγ were measure by DNA gel. (B) Male 6-10 weeks WT mice and *REGγ*^{-/-} mice were injected with 10 mg/kg cisplatin intraperitoneally. The tissue injury of small intestine, kidney and lung were exhibited by H&E staining. (C) The number of macrophages in spleen from WT mice and *REGγ*^{-/-} mice injected with cisplatin. (D) The weight loss of WT mice and *REGγ*^{-/-} mice injected with 10 mg/kg cisplatin intraperitoneally from first day to the fifth day. (E) The expression of REGγ in the lung from WT mice and *REGγ*^{-/-} mice injected with cisplatin. (F) The expression of REGγ in the kidney from WT mice and *REGγ*^{-/-} mice injected with cisplatin. Differences were measured by T test. ns, not significant, *P < 0.05, **P < 0.01, ***P < 0.001.



Supplementary Figure 5. The expression of REG γ in small intestine in CLP-induced sepsis mice. (A) The expression of REG γ in small intestine from WT mice with CLP operation.

Movie S1. Cell morphology of HeLa shN cell under cisplatin stimulation with PI staining

Movie S2. Cell morphology of HeLa sh*REGγ* cell under cisplatin stimulation with PI staining