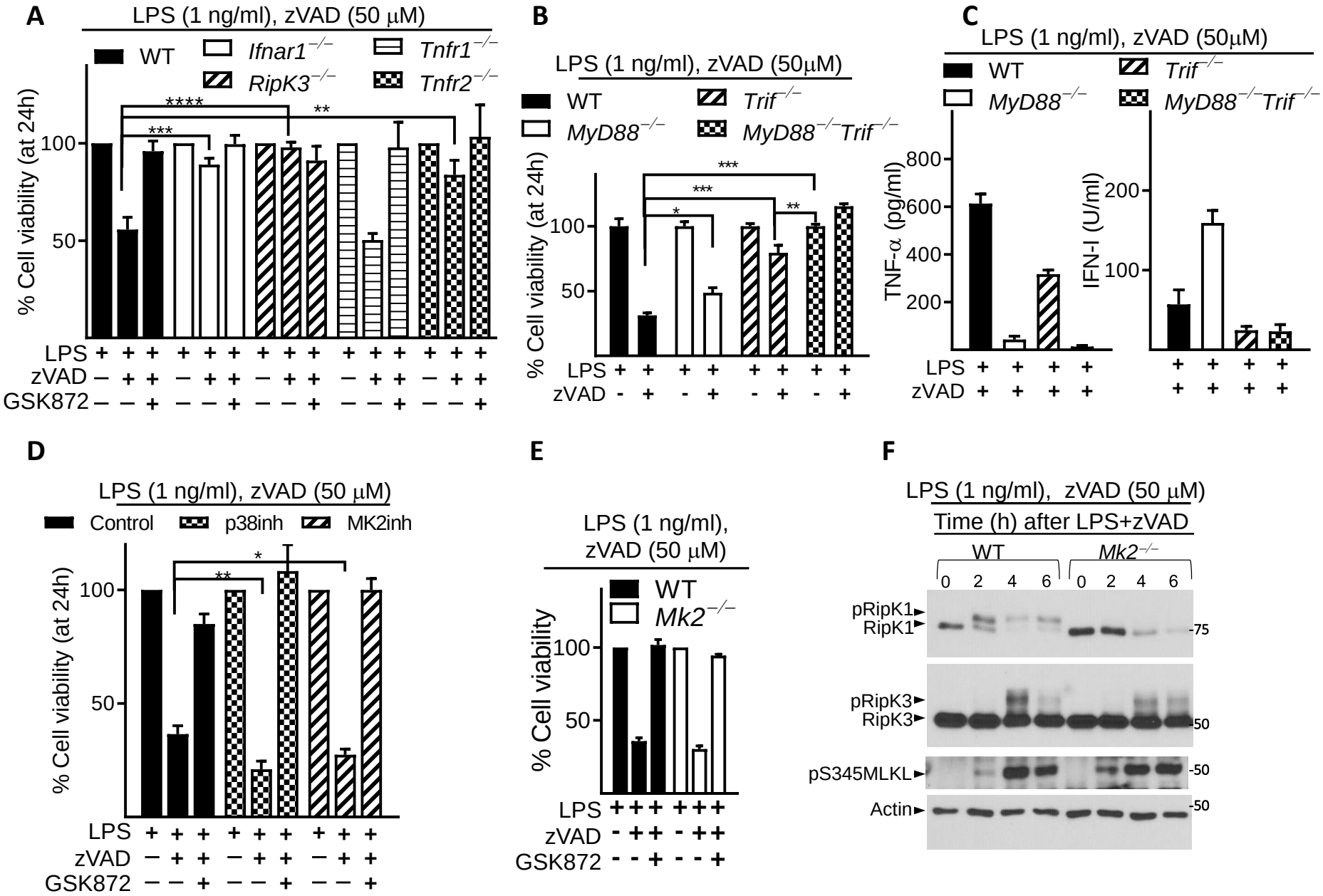

Figure S1: Related to Figure 1. MyD88 and TRIF promote necroptosis of macrophages in response to reduced LPS concentration. (**A-F**) BMMs were generated from WT and various knockout mice indicated in the figure and treated with a reduced concentration (1 ng/ml) of LPS and zVAD-fmk (50 μM), and cell death was evaluated at 24h by MTT assay (**A, D, E**) or by Alamar blue assay (**B**). Production of TNFα (ELISA) and IFN-I (bioassay) was measured in cell supernatants collected at 24h (**C**). Cells were also treated with LPS and zVAD-fmk as mentioned above and $p38^{MAPK}$ inhibitor (LY2228820, 4 μM) or MK2 inhibitor (PF3644022, 5 μM) (**D**), and cell death was evaluated at 24h by MTT assay. Cell extracts were collected at various time intervals and the expression/activation of various proteins evaluated by western blotting (**F**). Graphs show the percentage of viable cells ± SD relative to controls. Representative data of one experiment of three similar experiments is show. Each experiment was repeated three times. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

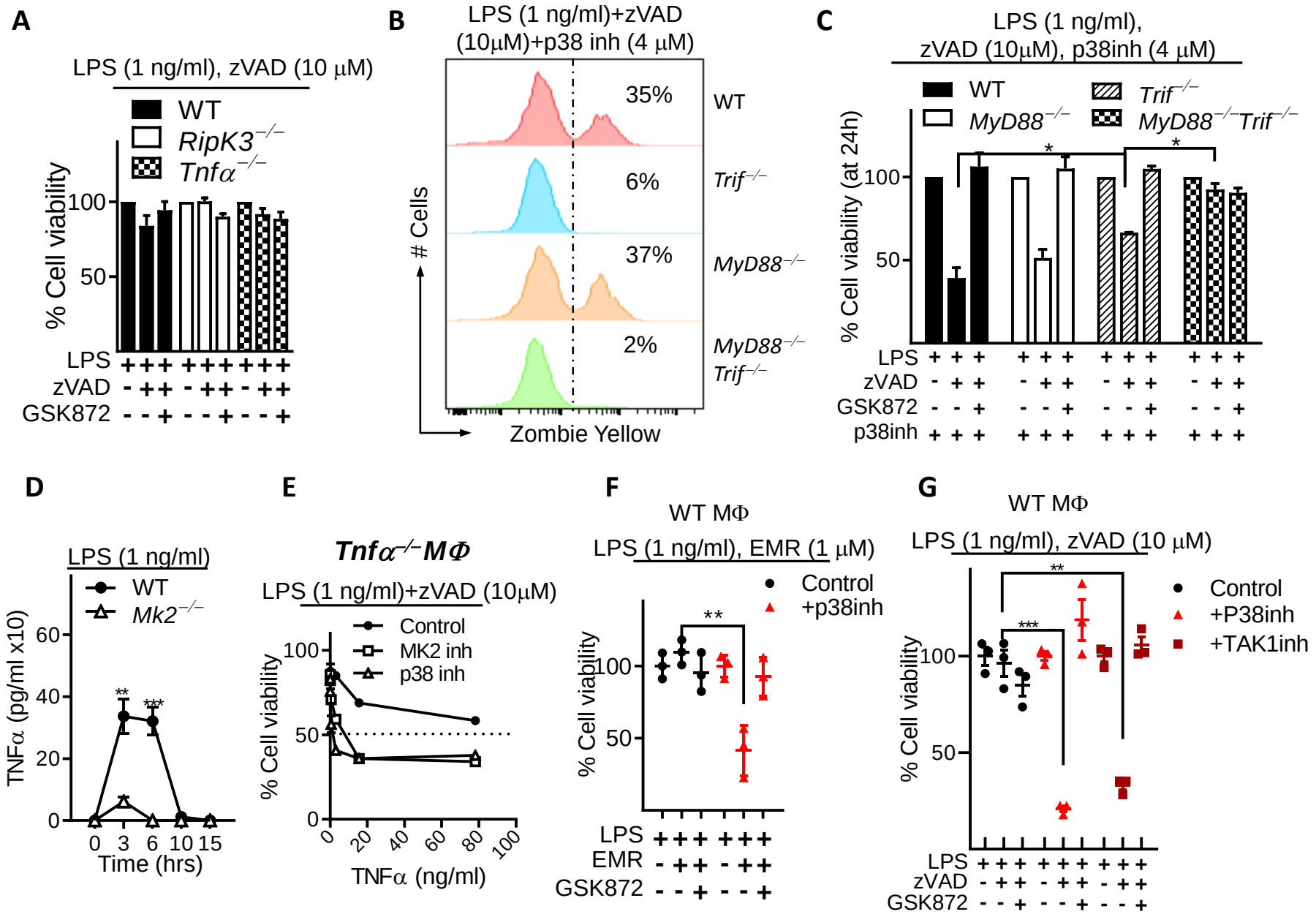

Figure S2: Related to Figure 2, 3. Induction of cell death at reduced LPS and zVAD concentrations requires both TRIF and MyD88 signaling. (**A-E, G**) BMMs were generated from WT and/or various knockout mice indicated in the figure and treated with LPS (1 ng/ml) and a reduced concentration (10 μM) of zVAD-fmk, and cell death was evaluated at 24h by MTT assay (**A**), or at 6h by Zombie Yellow assay (**B**), or by 24 h by Alamar blue assay (**C**), or by CCK-8 assay (**G**). In some experiments, cells were also co-treated with inhibitors against p38 (LY2228820, 4 μM) (**B, E**), MK2 (PF3644022, 5 μM) (**E**) and TAK1 ((5*Z*)-7-Oxozeaenol, 100 nM) (**G**). Expression of TNFα was measured in the supernatants collected at various time intervals after stimulation of WT or *Mk2*$^{-/-}$ macrophages with LPS (1 ng/ml) (**D**). *Tnfα*$^{-/-}$ macrophages were stimulated with LPS (1 ng/ml) + zVAD-fmk (10 μM) and different concentrations of recombinant TNFα +/- p38^{MAPK}/MK2 inhibitors, and cell death was evaluated by MTT assay at 24h (**E**). BMMs from WT mice were treated with LPS (1 ng/ml) and a reduced concentration (1 μM) of Emricasan (EMR) +/- p38^{MAPK} inhibitor (LY2228820, 4 μM) +/- RipK3 inhibitor (GSK872, 4 μM), and cell death was evaluated 24h later by CCK8 assay (**F**). Representative data of one experiment of three similar experiments is show. Graphs show the percentage of viable cells ± SD relative to controls. Each experiment was repeated three times. *P < 0.05, **P < 0.01, ***P < 0.001.

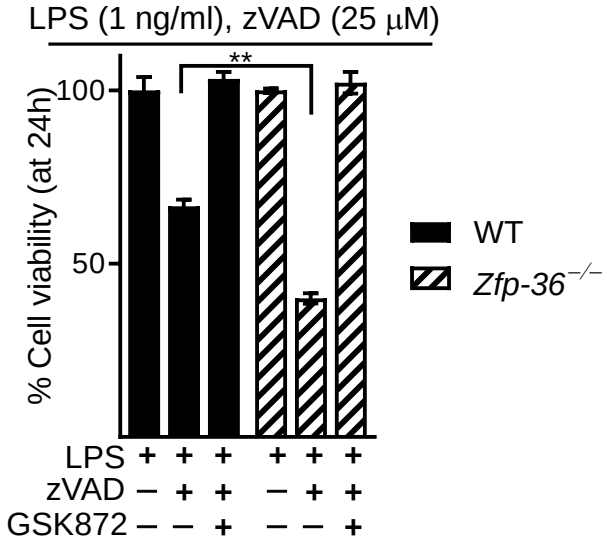

Figure S3: Related to Figure 3. *Zfp-36* inhibits necroptosis at higher concentration of LPS. WT and *Zfp-36*$^{-/-}$ macrophages were stimulated with LPS (1 ng/ml) and zVAD-fmk (25 μM), and cell death was evaluated by MTT assay at 24 h. Representative data of one experiment of three similar experiments is shown. Graphs show the percentage of viable cells ± SD relative to controls. Each experiment was repeated three times. **P < 0.01.

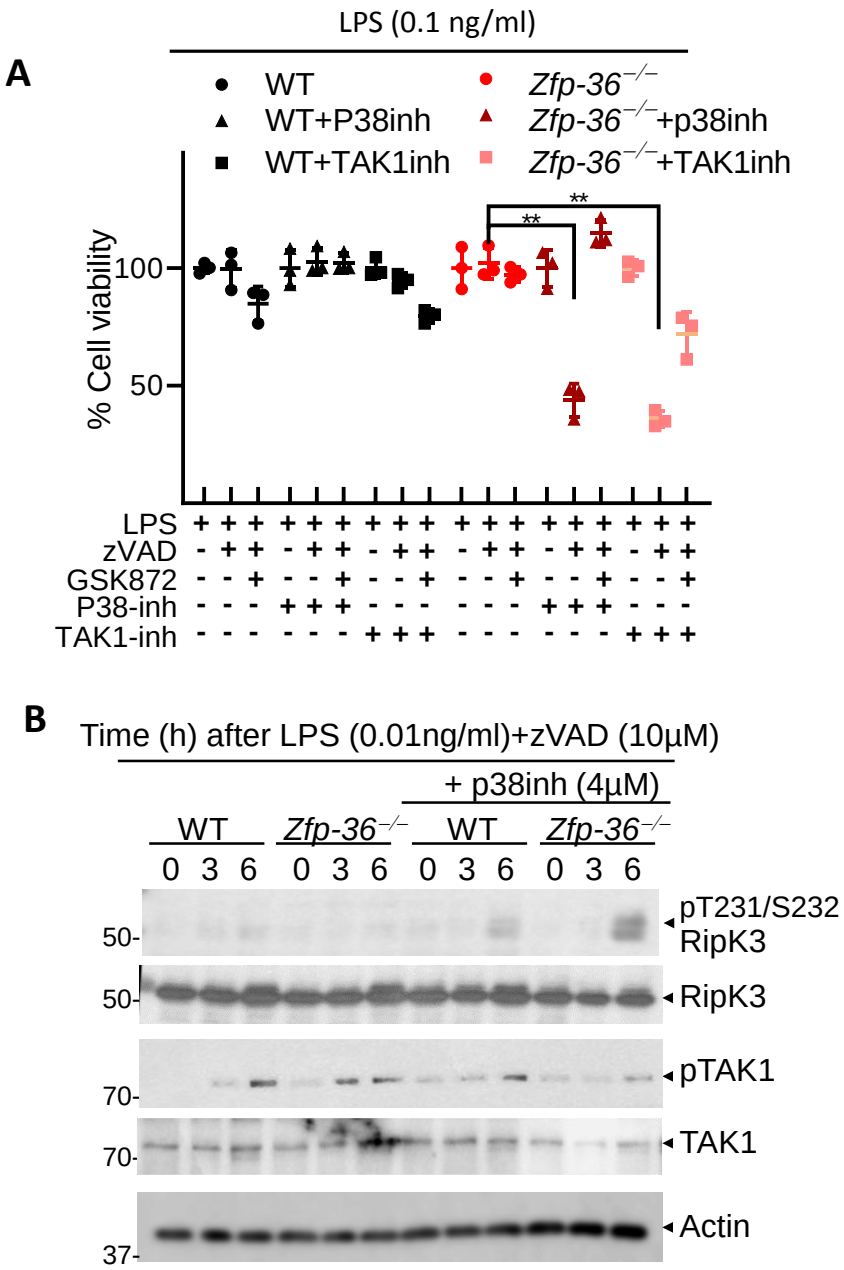

Figure S4: Related to Figure 3 and 4. *Zfp-36* inhibits necroptosis which is blocked by TAK1 and p38^{MAPK}. WT and *Zfp-36*$^{-/-}$macrophages were stimulated with LPS (0.01 ng/ml) and zVAD-fmk (10 μM)+/- p38 inhibitor (LY2228820, 4 μM) +/- TAK1 inhibitor ((5Z)-7-Oxozeaenol, 100 nM). Cell death was evaluated by CCK8 assay at 24 h (**A**), and western blotting of cell extracts was performed at various time intervals (**B**). Representative data of one experiment of three similar experiments is shown. Graphs show the percentage of viable cells ± SD relative to controls. Each experiment was repeated three times. **P < 0.01.