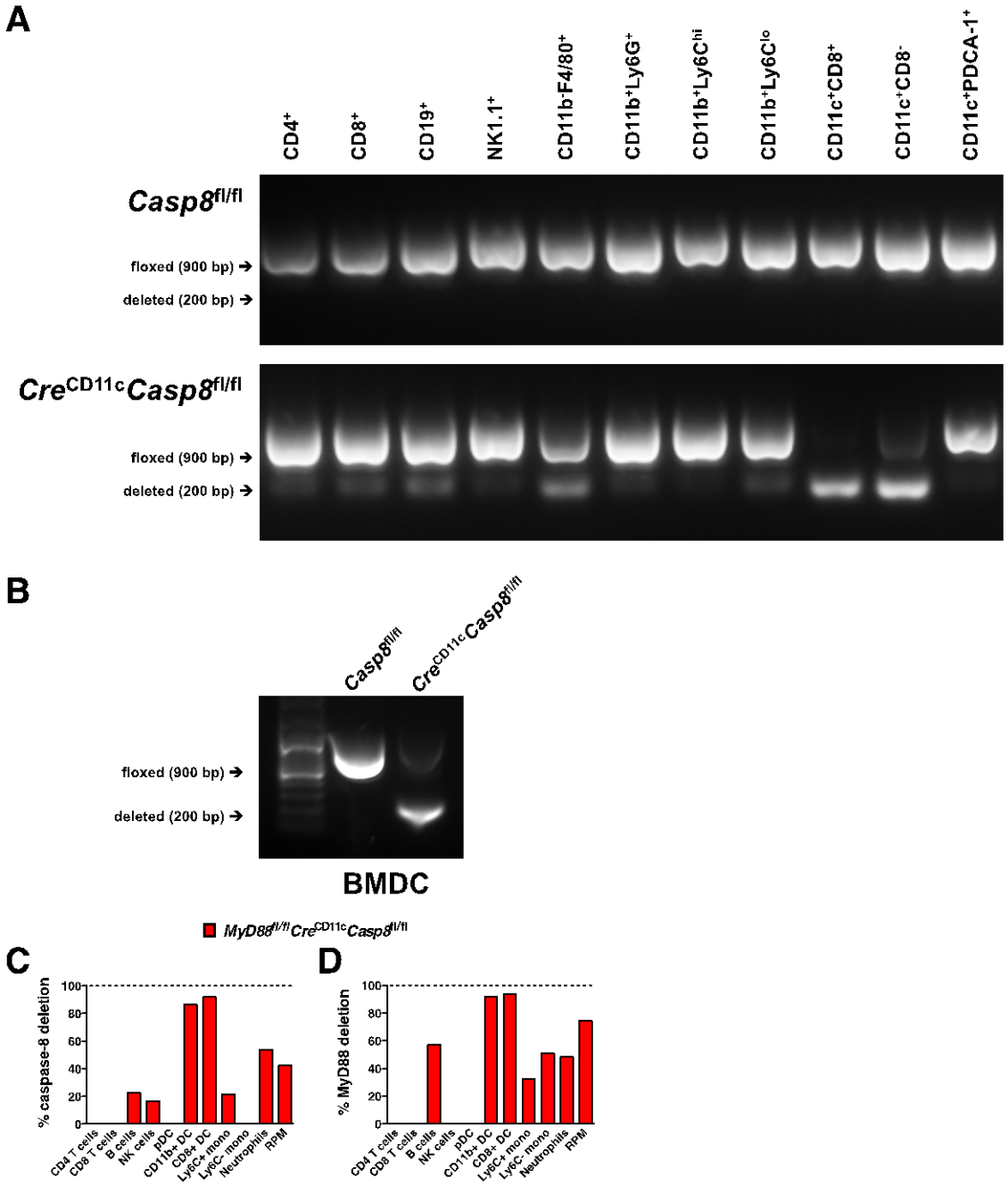
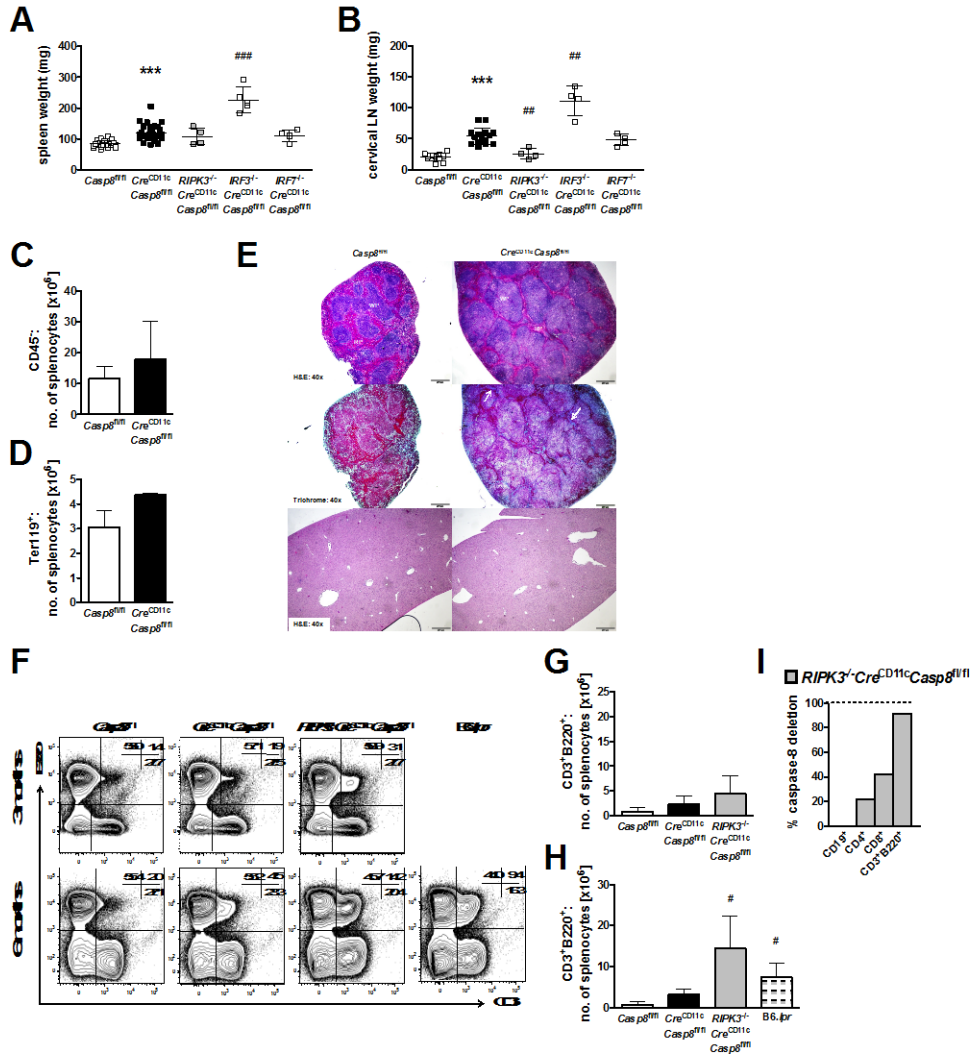
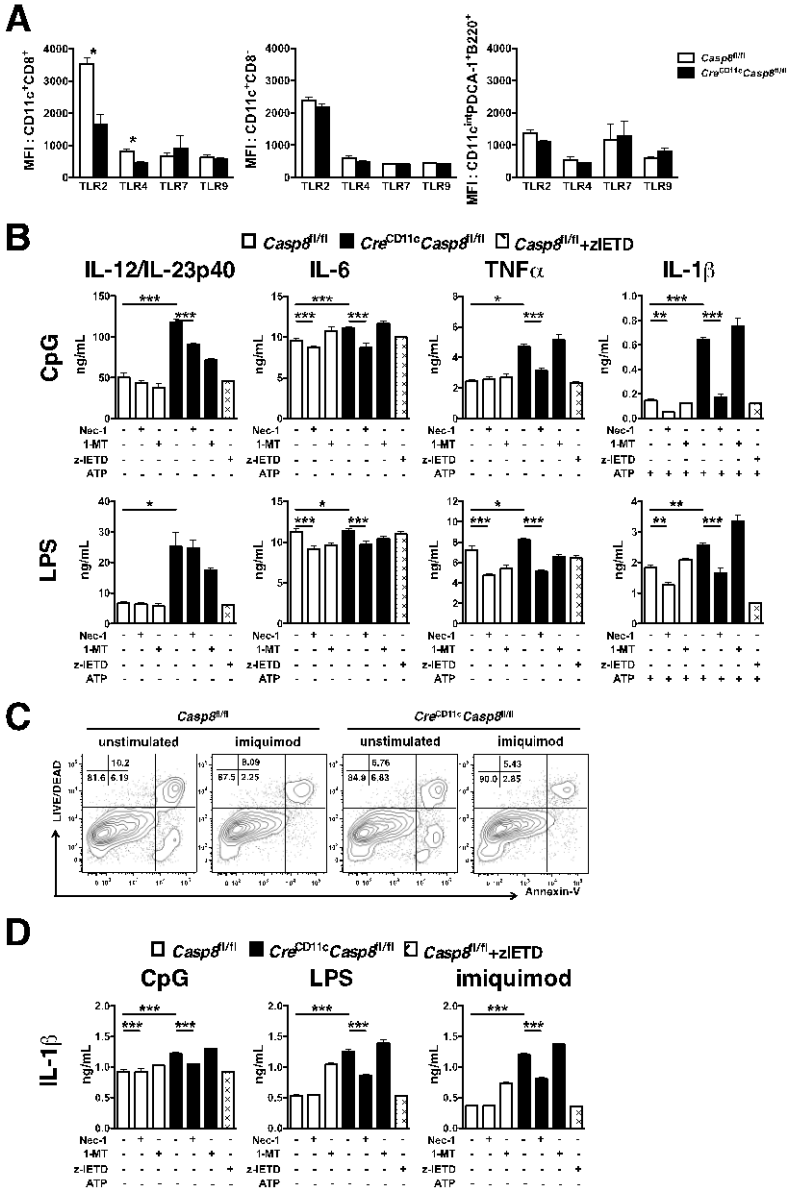


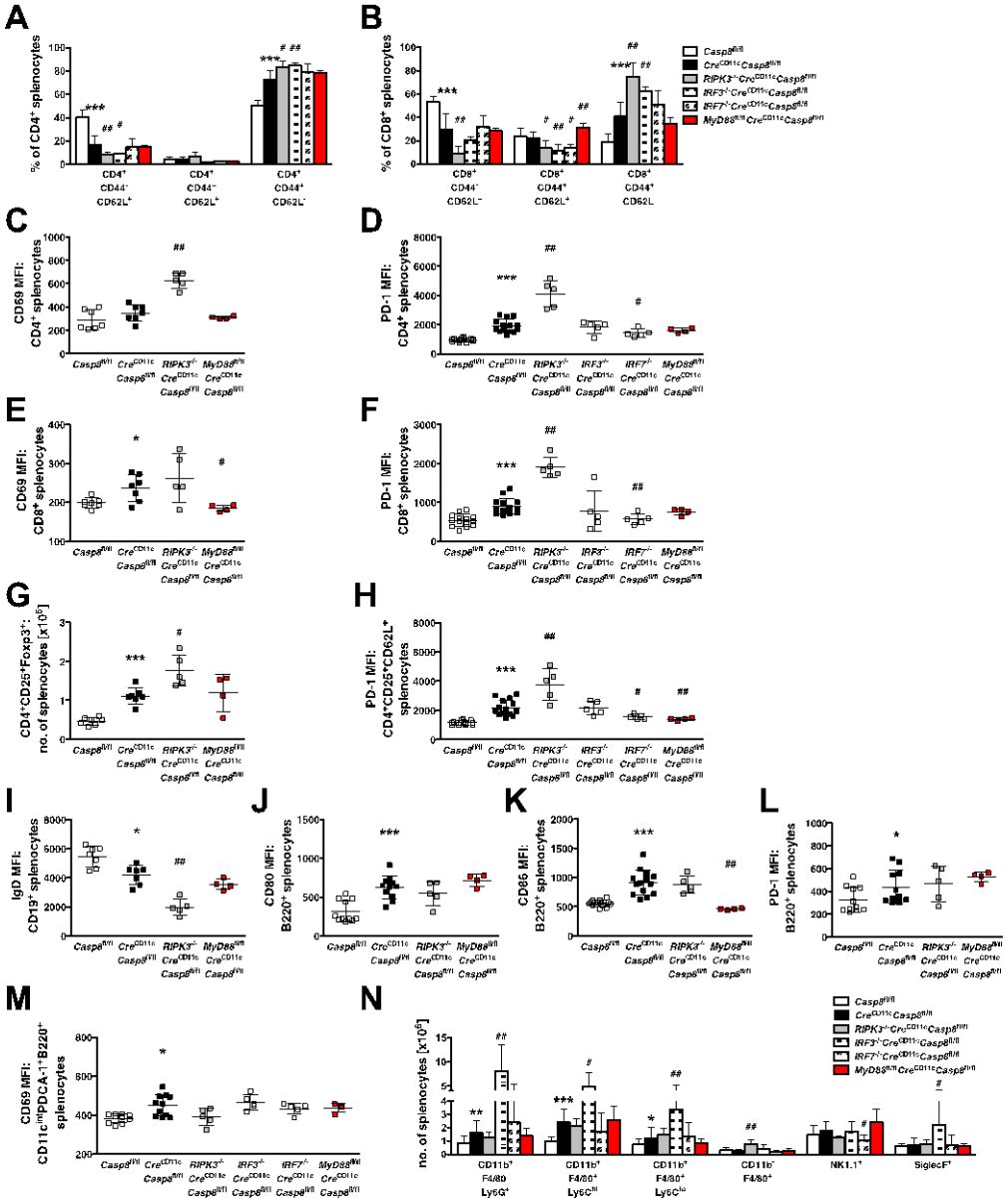
Supplemental Figure 1. PCR for genotype validation. (**A**) Splenocyte populations from *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice were sorted as: B cells (CD19^{+}), CD4^{+} and CD8^{+} T cells, NK cells (NK1.1^{+}), red pulp macrophages (CD11b^{+}F4/80^{+}), neutrophils (CD11b^{+}Ly6G^{+}), monocytes/macrophages (CD11b^{+}CD11c$^{low/negative}$SSC^{low}F4/80^{low}) further subdivided into Ly6C^{-} and Ly6C^{+}, pDC (mPDCA-1^{+}B220^{+}CD11c^{intermediate}) and conventional DC (B220^{-}CD11c^{+}CD8^{+} and B220^{-}CD11c^{+}CD8^{-}), and subjected to PCR for *Casp8*^{floxed} and *Casp8*^{deleted} alleles. (**B**) BMDCs generated from *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice were subjected to PCR for *Casp8*^{floxed} and *Casp8*^{deleted} alleles. (**C**-**D**) Splenocyte populations from *MyD88*$^{fl/fl}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice were sorted as in (**A**) and subjected to real time PCR for (**C**) *caspase-8* and (**D**) *MyD88* deletion.



Supplemental Figure 2. Phenotypes of young and aged mice. (**A-B**) 2-3-month-old female *Casp8*$^{fl/fl}$ (control), *Cre*^{CD11c}*Casp8*$^{fl/fl}$, *RIPK3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$, *IRF3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ and *IRF7*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice (n≥4) were evaluated for (**A**) spleen and (**B**) cervical lymph node weights. (**C-E**) 6-8-month-old control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice (n≥7) were evaluated for numbers of (**C**) CD45$^-$ and (**D**) Ter119$^+$ splenocytes. (**E**) Representative formalin-fixed spleen sections (4 μm) stained with hematoxylin and eosin (H&E) and trichrome and formalin-fixed liver sections (4 μm) stained with H&E. (**F-H**) Splenocytes from 3- and 6-month-old control, *Cre*^{CD11c}*Casp8*$^{fl/fl}$, *RIPK3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ and B6.*lpr* mice (n≥5) were analyzed by flow cytometry. (**F**) Representative CD4$^-$CD8$^-$CD3$^+$B220$^+$ T-cell percentages of total splenocytes at 3 and 6 months. Numbers of CD4$^-$CD8$^-$CD3$^+$B220$^+$ double negative T-cells at (**G**) 3 and (**H**) 6 months. (**I**) Splenocyte populations were sorted as: B-cells (CD19$^+$), CD4$^+$, CD8$^+$ and DN T-cells (CD4$^-$CD8$^-$CD3$^+$B220$^+$) and subjected to real time PCR for *caspase-8* deletion. Data are represented as mean ± SD and compared by Mann Whitney test. * denotes comparison between control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$, # denotes comparison between *Cre*^{CD11c}*Casp8*$^{fl/fl}$ and *RIPK3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$, B6.*lpr*, *IRF3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ or *IRF7*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$. *, #:p<0.05; **, ##:p<0.005; ***, ###:p<0.0005.



Supplemental Figure 3. TLR ligation does not induce cell death. (**A**) Splenocytes from 6-8 month-old *Casp8*$^{fl/fl}$ (control) and *Cre*^{CD11c}*Casp8*$^{fl/fl}$ (n≥5) were analyzed by flow cytometry for expression of TLRs. (**B**) GM-CSF + Flt3-L-treated BMDCs from control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice were stimulated with CpG or LPS ± Nec-1 and/or zIETD-FMK (zIETD), a caspase-8 inhibitor and/or 1-Methyl-D-tryptophan (1-MT) for 6 hours ± ATP (5mM) and supernatants evaluated for IL-12/IL-23p40, IL-6, TNFα, and IL-1β. (**C**) Control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$ BMDCs were stimulated with imiquimod (5 μg/mL) for 6 hours and cells were stained with Annexin-V and Aqua live/dead. Representative percentages of Annexin-V- and LIVE/DEAD-stained BMDCs. (**D**) GM-CSF + Flt3-L-treated BMDCs from control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice were stimulated with CpG, LPS or imiquimod ± Nec-1 and/or zIETD-FMK (zIETD) and/or 1-Methyl-D-tryptophan (1-MT) for 6 hours ± ATP (5mM) and supernatants evaluated for IL-1β. Data are represented as mean ± SD and compared by Mann Whitney test.



Supplemental Figure 4. Alterations in splenic populations. (**A-L**) Splenocytes from 6-8-month-old *Casp8*$^{fl/fl}$ (control), *Cre*^{CD11c}*Casp8*$^{fl/fl}$, *RIPK3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$, *IRF3*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ and *IRF7*$^{-/-}$*Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice (n≥4) were analyzed by flow cytometry. Naive (CD44^{-}CD62L^{+}), memory (CD44^{+}CD62L^{+}) and effector (CD44^{+}CD62L^{-}) (**A**) CD4+ T-cell and (**B**) CD8^{+} T-cell numbers. CD4^{+} (**C**) CD69 and (**D**) PD-1 expression levels and CD8^{+} T-cell (**E**) CD69 and (**F**) PD-1 expression levels. Regulatory T-cell (CD4^{+}CD25^{+}Foxp3^{+}) (**G**) numbers and (**H**) PD-1 expression level. Total B-cell (**I**) IgD, (**J**) CD80, (**K**) CD86 and (**L**) PD-1 expression levels. (**M**) plasmacytoid DC (CD11c^{int}PDCA-1^{+}B220^{+}) CD69 expression. (**N**) Neutrophil (CD11b^{+}F4/80^{-}Ly6G^{+}), Ly6C^{high} macrophage (CD11b^{+}F4/80^{+}), Ly6C^{low} macrophage (CD11b^{+}F4/80^{+}), red pulp macrophage (CD11b^{+}F4/80^{-}), NK (NK1.1^{+}) and eosinophil (SiglecF^{+}) cell numbers. Data are represented as mean ± SD and compared by Mann Whitney test. * denotes comparison between control and *Cre*^{CD11c}*Casp8*$^{fl/fl}$, # denotes comparison between *Cre*^{CD11c}*Casp8*$^{fl/fl}$ and experimental knockouts. *, #:p<0.05; **, ##:p<0.005; ***, ###:p<0.0005.