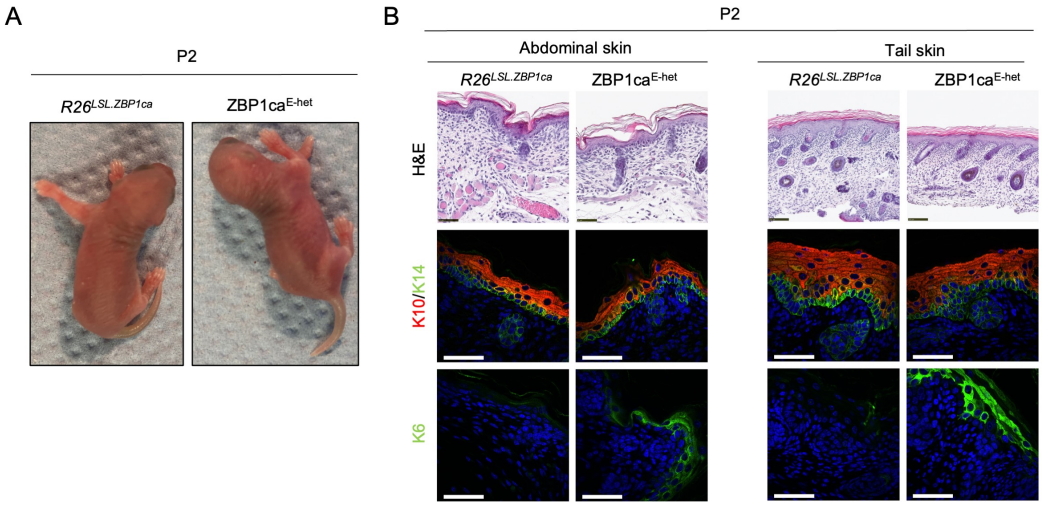

Figure S1. ZBP1ca-driven tail skin inflammation starts at postnatal day 2
(A) Representative photographs of ZBP1ca$^{E\text{-}het}$ mouse (n=7) and control littermate (n=12) at P2. **(B)** Representative images from skin sections of ZBP1ca$^{E\text{-}het}$ mice and littermate at P2 stained with H&E (Scale bars=50 µM, n=6 for ZBP1ca$^{E\text{-}het}$, n=5 for control) or immunostained with K10, K14 and K6 (Scale bars=50 µM, n=4 for ZBP1ca$^{E\text{-}het}$, n=4 for *R26*$^{LSL.ZBP1ca}$).

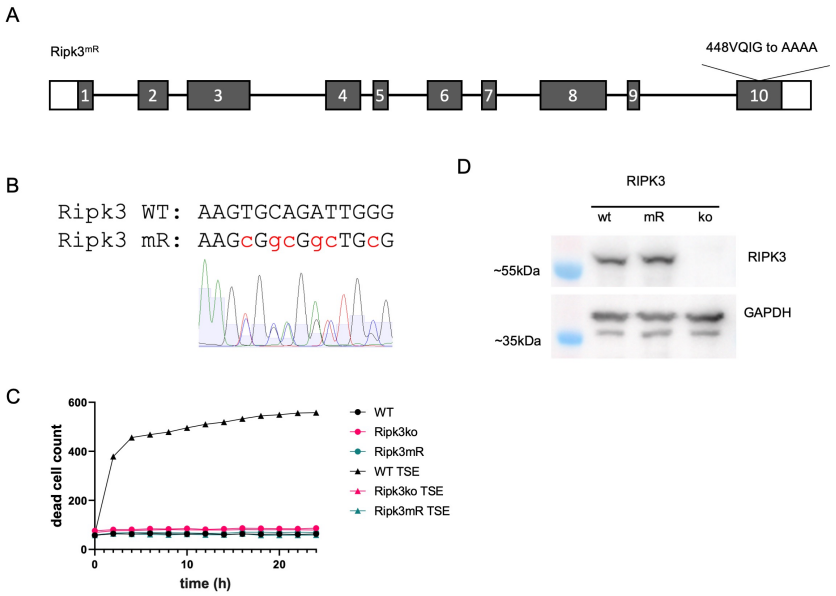

Figure S2. Generation of *Ripk3*^{mR} mice. (A) The core RHIM motif in exon 10 of the *Ripk3* gene was altered from the amino acid sequence VQIG to AAAA using CRISPR/Cas9 technology with the gRNA target sequence 5'ACTGTTCTGAAGTGCAGATT3' and the repair ssODN
5'CACCATCACCTCCTCCTTTCCTCTTAAAGGGCCACCGGCTCTCGTCTTCAACAACTGT TCTGAAGCGGCGGCTGCGAACTACAACTCCTTGGTAGCACCACCAAGAACTACTGCCT CAAGTTCGGCCAAGTATGACCAAG3' **(B)** Sanger sequencing indicates the desired mutations in heterozygous *Ripk3*$^{mR/WT}$ mice with the mutated nucleotides indicated in red **(C)** Nucleotide substitutions did not abrogate protein expression, as demonstrated by western blotting of primary lung fibroblasts (LFs) with *Ripk3*$^{ko/ko}$ cells as a control **(D)** Necroptosis induction by combined treatment with TNF (T), smac mimetic (S) and Emricasan (E) in primary LFs revealed, that *Ripk3*$^{mR/mR}$ cells are resistant to this form of cell death, as assessed by Incucyte-based life cell imaging

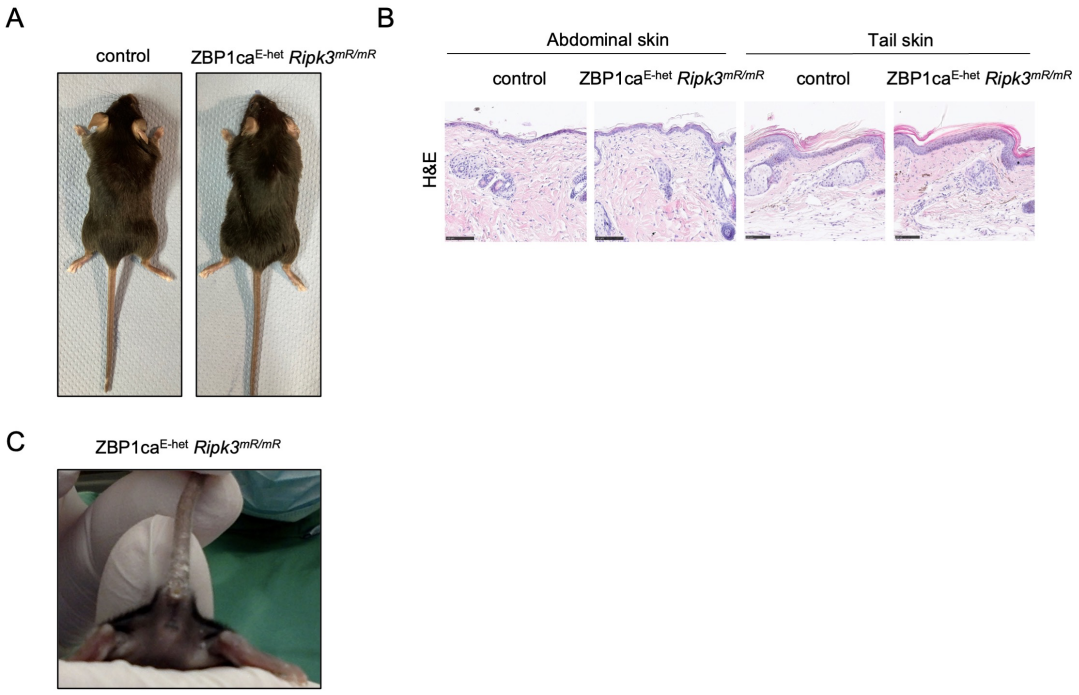

Figure S3. ZBP1ca$^{E\text{-}het}$ *Ripk3*$^{mR/mR}$ mice can age at least up to 30 weeks of age.
(A) Representative photographs of ZBP1ca$^{E\text{-}het}$ *Ripk3*$^{mR/mR}$ mouse (n=12) and control (n=3) at 30 weeks of age **(B)** Representative images from skin sections of ZBP1ca$^{E\text{-}het}$ *Ripk3*$^{mR/mR}$ mice and littermate at 30 weeks of age stained with H&E (Scale bars=100 μM, n=6 for ZBP1ca$^{E\text{-}het}$ *Ripk3*$^{mR/mR}$, n=3 for control). **(C)** Representative photograph of ZBP1ca$^{E\text{-}het}$ *Ripk3*$^{mR/mR}$ mouse at P14.

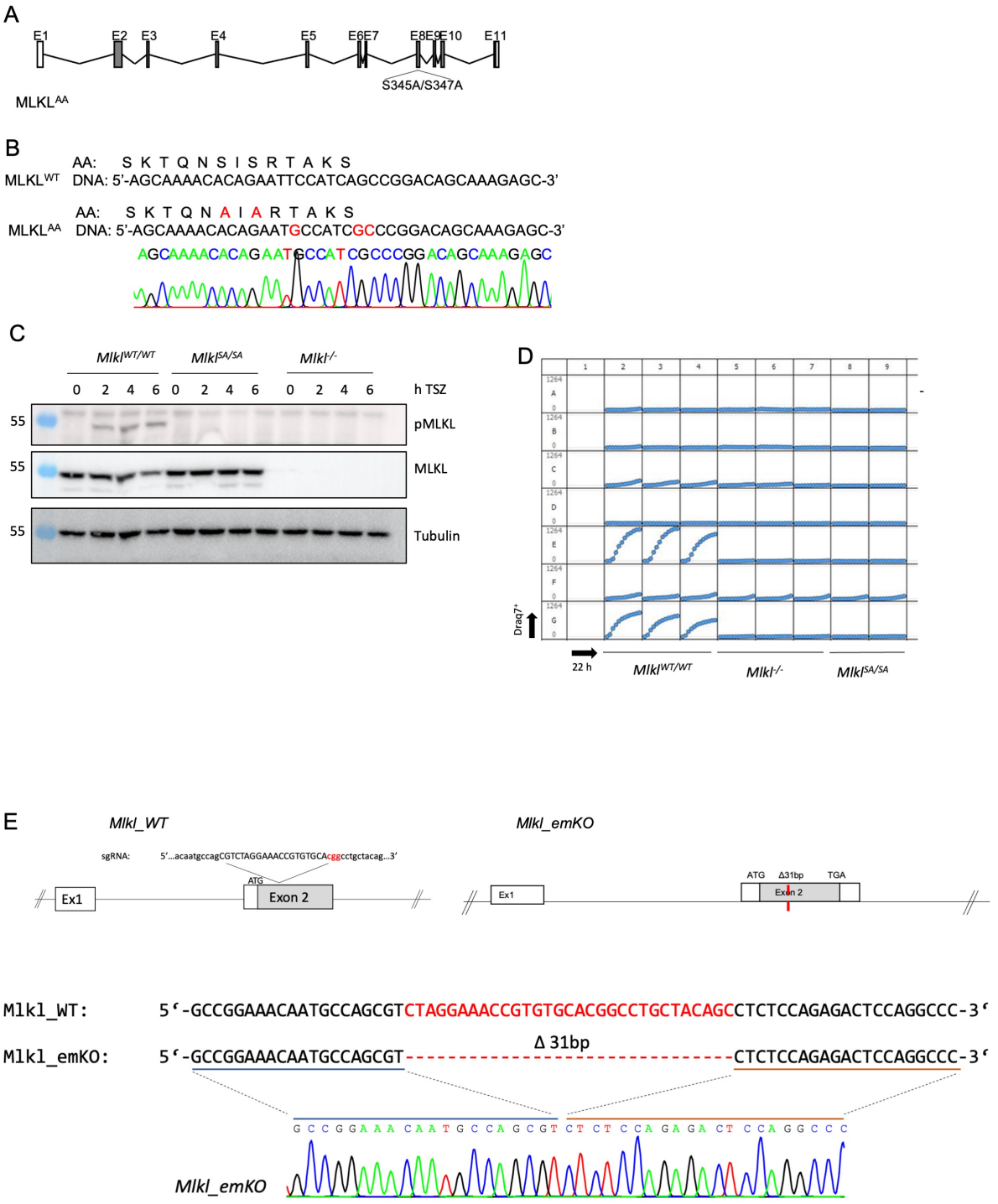

Figure S4. Generation of Mlkl mutant mice

(A) Serines at positions 345 and 347 encoded from exon 8 in the mouse Mlkl gene were mutated to alanine using CRISPR/Cas9 technology with the gRNA target sequence 5' AAACACAGAATTCCATCAGC3' and the ssODN repair template 5' AACGTCTGCATCTAACACATCTGTCTGTCTAGCTTGCAGGATTTGAGTTAAGCAAAACAC AGAATGCCATCGCCCGGACAGCAAAGAGCACTAAAGCAGAGAGATCCAGTTCAACGAT ATATGTCTCCCCTGAGAGAC3' to generate the *Mlkl*^{AA} mice **(B)** Successful generation of the *Mlkl*^{AA} allele was assessed by sanger sequencing; red nucleotides (DNA) and amino acids (Prot.) indicate the desired mutations that are visible on the sequencing trace from a homozygous Mlkl$^{AA/AA}$ mouse **(C)** Expression of total MLKL and pMLKL protein was assessed by western blot after TNF (T), Smac mimetic (S) and Z-VAD-FMK (Z) stimulation with tubulin

as a loading control **(D)** Incucyte based life cell microscopy analysis of cell death in Mlkl$^{WT/WT}$, MLKL$^{emKO/emKO}$ and Mlkl$^{AA/AA}$ cells upon stimulation with TNF (T), Smac mimetic (S) and Emricasan, with total count of dead cells (Draq7+) displayed over time d). The Mlkl^{emKO} allele was generated using CRISPR/Cas9 technology and a single sgRNA binding in Exon2 of the mouse Mlkl gene a). The resulting Mlkl^{emKO} allele resulted from a 31 bp deletion (visible in the sanger sequencing trace of a homozygous mouse) that caused a frameshift and premature stop codon (TGA) in exon2.

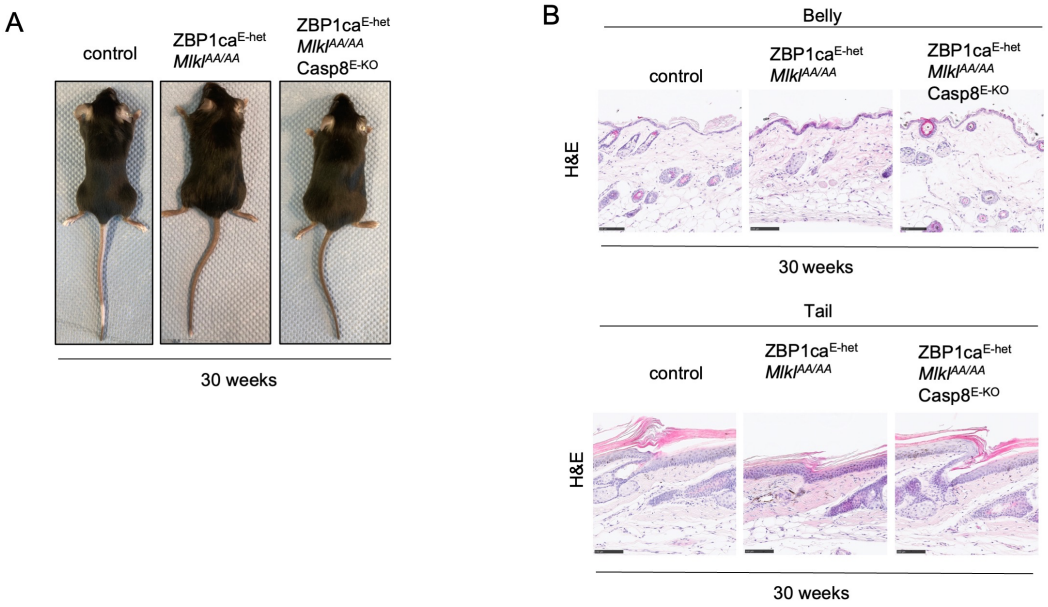

Figure S5. ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$* and ZBP1ca *Mlkl$^{AA/AA}$* Casp8$^{E\text{-}KO}$ mice can age at least up to 30 weeks of age. (A) Representative photographs of ZBP1ca$^{E\text{-}het}$ *Mlkl$^{SA/SA}$* (n=12), ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$* Casp8$^{E\text{-}KO}$ (n=13) and control (n=13) at 30 weeks of age). **(B)** Representative images from abdominal and tail skin sections of ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$*, ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$* Casp8$^{E\text{-}KO}$ mice and control at 30 weeks of age stained with H&E (Scale bars=100 µM, n=5 for ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$*, n=3 for ZBP1ca$^{E\text{-}het}$ *Mlkl$^{AA/AA}$* Casp8$^{E\text{-}KO}$, n=4 for control)