Figure S1

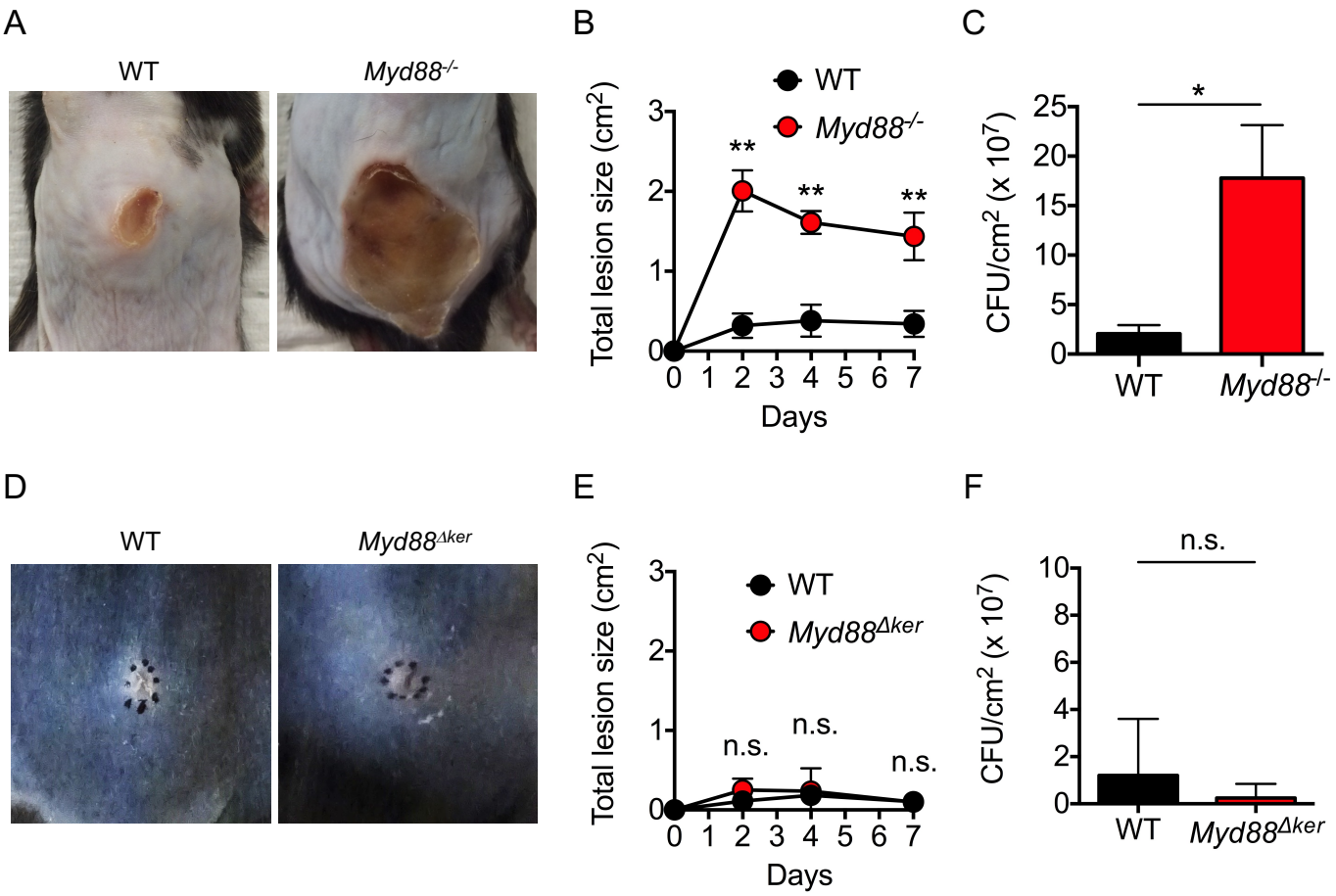

Figure S1. *Myd88*$^{-/-}$ mice show increased skin lesions and pathogen loads after intradermal *S. aureus* infection. Related to Figure 1.
A, WT and *Myd88*$^{-/-}$ mice were intradermally inoculated with *S. aureus*. Representative macroscopic images of mice colonized with *S. aureus* 7 days after infection (n=4 mice per group). **B-C**, Skin lesion size (**B**) of indicated time point. *S. aureus* CFU in the skin (**C**) of WT and *Myd88*$^{-/-}$ mice 7 days after infection. **D**, WT and *Myd88*$^{\Delta ker}$ mice were intradermally inoculated with *S. aureus*. Representative macroscopic images of mice colonized with *S. aureus* 7 days after infection (n=4 to 7 mice per group). **E-F**, Skin lesion size (**E**) at indicated time point. *S. aureus* CFU in the skin (**F**) of WT and *Myd88*$^{\Delta ker}$ mice 7 days after infection. Data are presented as mean ± SD. Data are representative of 2 independent experiments. n.s.; not significant, *P<0.05 and **P<0.01, by unpaired two-tailed Mann-Whitney U test.

Figure S2

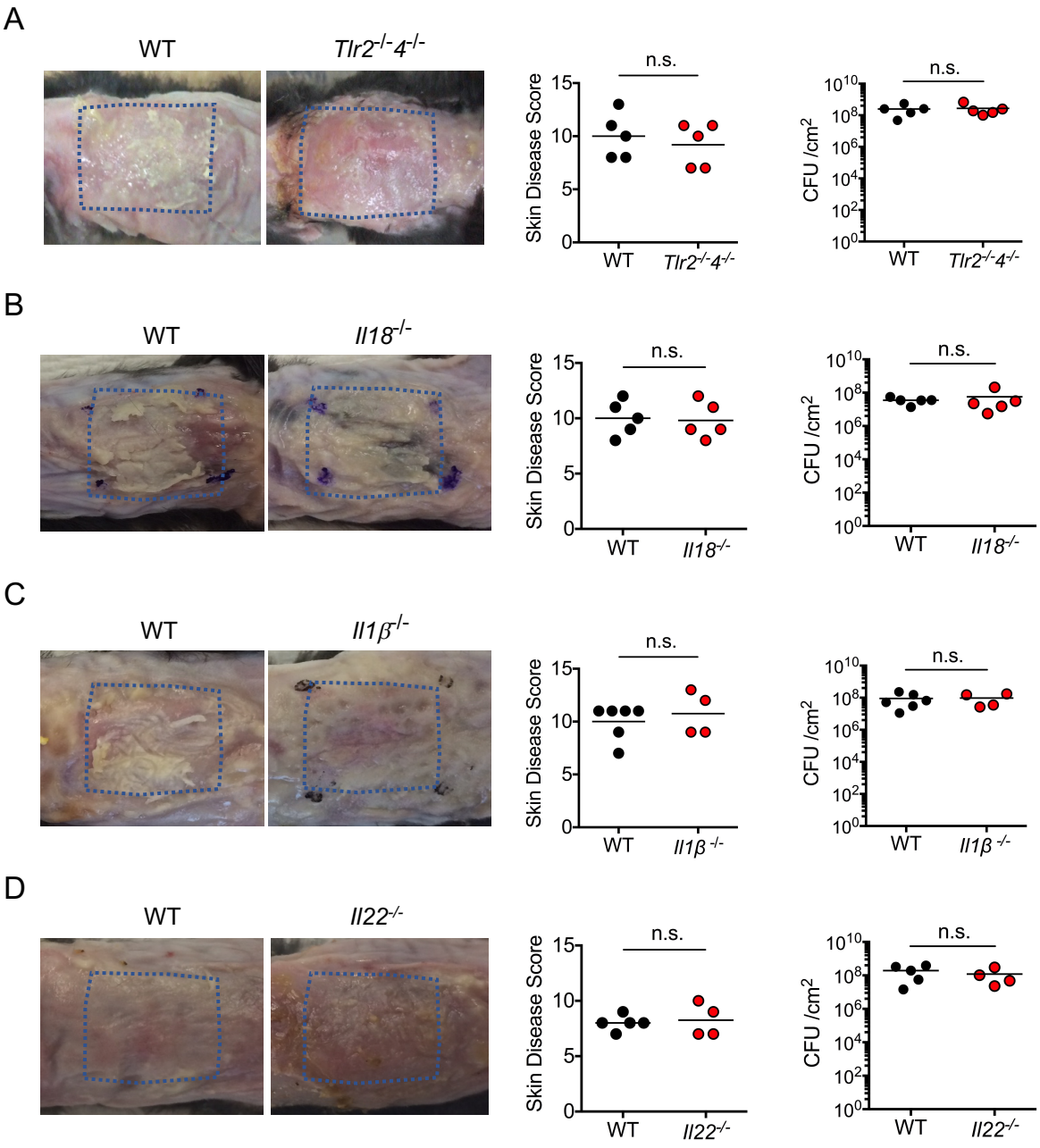

Figure S2. TLR 2/4, IL-1b, IL-18 and IL-22 are dispensable for *S. aureus*-induced skin inflammation. Related to Figure 2-4.

A-D, WT, *Tlr2*$^{-/-}$*4*$^{-/-}$ (**A**), *Il18*$^{-/-}$ (**B**), *Il1β*$^{-/-}$ (**C**) and *Il22*$^{-/-}$ mice (**D**) were epicutaneously colonized with *S. aureus*. Representative macroscopic images, skin disease scores and *S. aureus* CFU in the skin of the mice colonized with *S. aureus* (n=4 to 11 mice per group). Each dot represents a mouse. Data are representative of at least 2 independent experiments. ND; not detected, n.s.; not significant, by unpaired two-tailed Mann-Whitney U test.

Figure S3

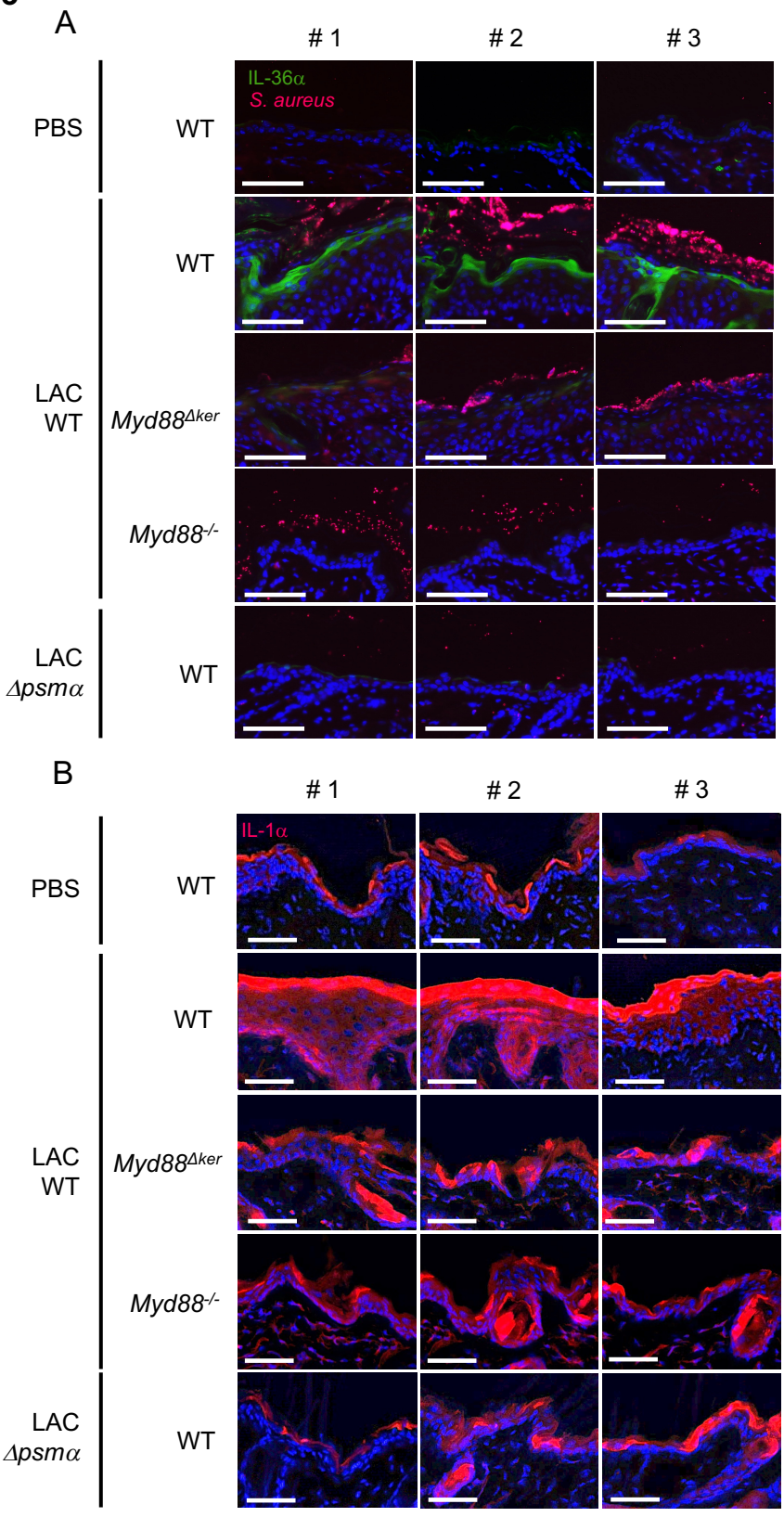

Figure S3. Expression of IL-1α and IL-36α in the skin of WT, *Myd88*$^{\Delta ker}$ and *Myd88*$^{-/-}$ mice infected epicutaneously with *S. aureus*. Related to Figure 3.
Representative slides from the skin of 3 different mice stained with Hoechst stain (blue) and antibodies against *S. aureus* (red) and IL-36α (green) (**A**) or Hoechst stain (blue) and antibody against IL-1α (red)(**B**). WT, *Myd88*$^{\Delta ker}$ and *Myd88*$^{-/-}$ mice colonized with *S. aureus* (LAC WT), WT mice with *Δpsmα S. aureus* (LAC *Δpsmα*) and WT mice treated with PBS are shown. Data are representative of at least 2 independent experiments. Scale bars, 50 μm.

Figure S4

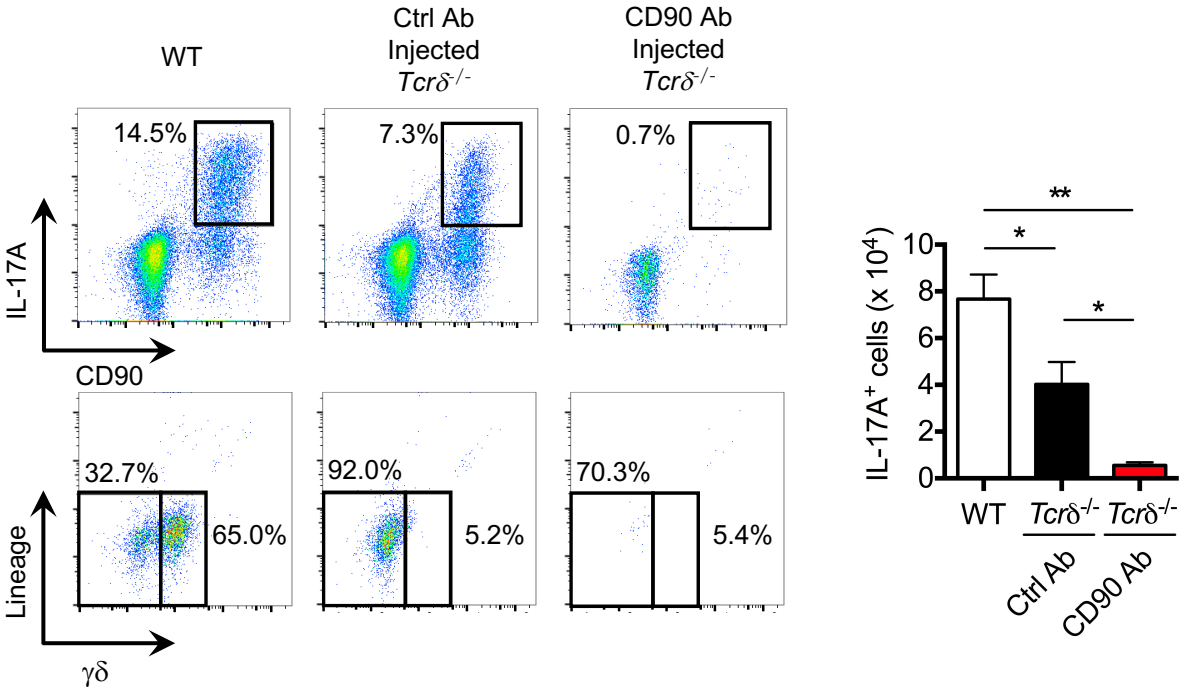

Figure S4. Administration of anti-CD90 Ab depletes IL-17 producers in *Tcrδ*$^{-/-}$ mice. Related to Figure 5.

IL-17A-producing cells were evaluated by flow cytometric analysis after epicutaneous *S. aureus* colonization in WT mice and *Tcrδ*$^{-/-}$ mice treated with controlAb and anti-CD90Ab. Representative flow cytometric analysis of lineage (B220, CD11b, CD11c, Gr-1, NK1.1)-negative cells and γδ T cells was performed on gated CD45+CD90+IL-17A+ skin cells (left panels) on day 7. Results in right panels represent mean ± SD of 3 experiments. The number of IL-17A+ cells in WT and *Tcrδ*$^{-/-}$ mice (right panels). *P<0.05, **P<0.01, by one-way ANOVA test with Bonferroni's correction.

Figure S5

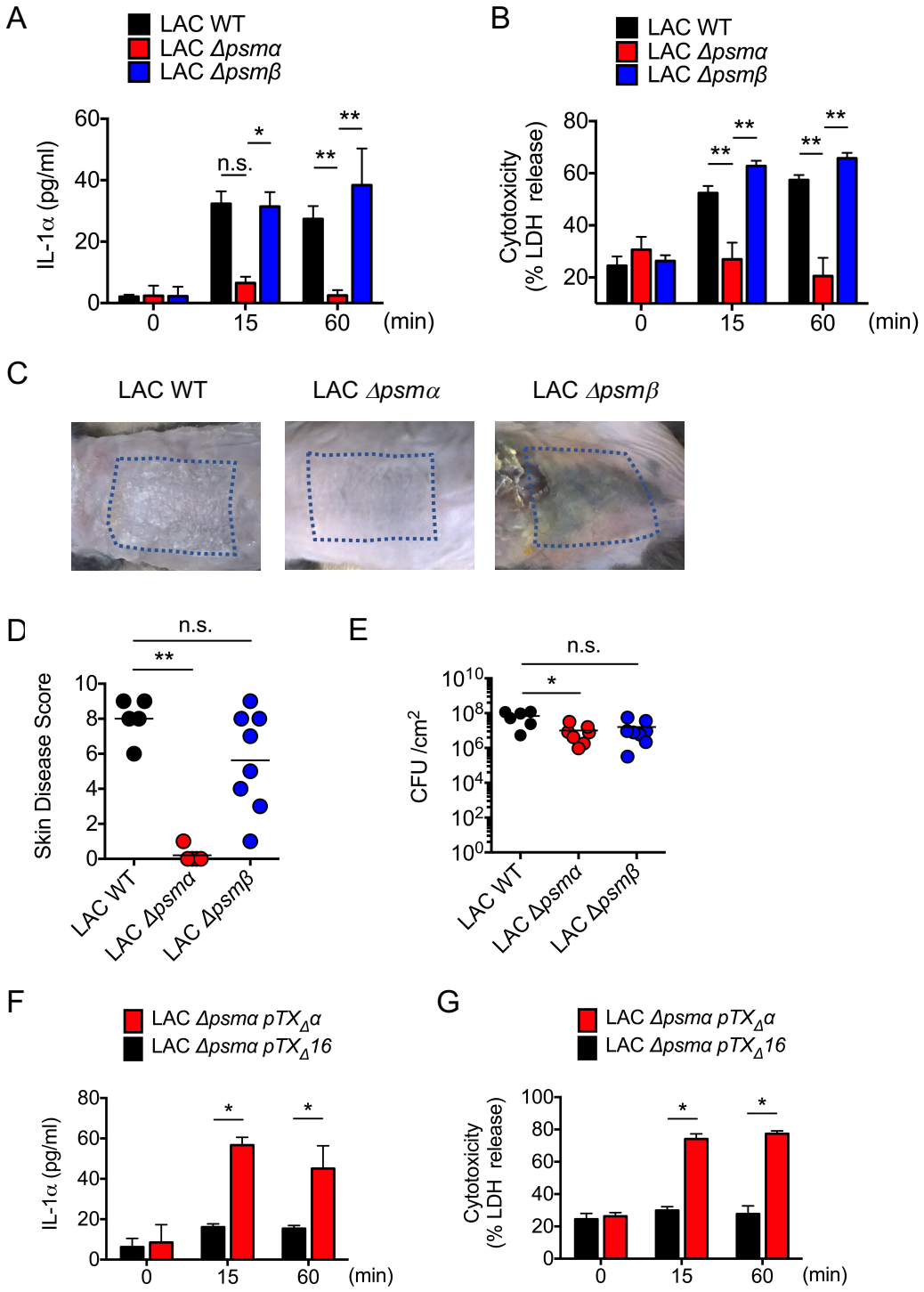

Figure S5. *S. aureus* PSMα, but not PSMβ, peptides induce cell death of murine keratinocytes and mediate skin inflammation. Related to Figure 6.

A-B, IL-1α release (**A**) and cytotoxicity (**B**) of murine primary KCs from WT mice stimulated with culture supernatant of LAC WT, LAC Δ*psmα*, or LAC Δ*psmβ*. Data are representative of 3 independent experiments. **C**, Representative macroscopic images of WT mice colonized with LAC WT, LAC Δ*psmα*, or LAC Δ*psmβ* on day 7 after colonization. **D-E**, Skin disease scores (**D**) and *S. aureus* CFU in the skin (**E**) of infected mice. Each dot represents an individual mouse. **F-G,** IL-1α release (**F**) and cytotoxicity (**G**) of murine primary KCs from WT mice stimulated with culture supernatant of Δ*psmα S. aureus* reconstituted with *psmα* plasmid (LAC Δ*psmα* pTX$_{\Delta}$*α*) or vector (LAC Δ*psmα* pTX$_{\Delta}$*16*). Data are combined of 2 independent experiments. n.s.; not significant, *P<0.05 and **P<0.01 by one-way ANOVA test with Bonferroni's correction (A, B), Kruskal-Wallis test (D, E) or unpaired two-tailed Mann-Whitney U test (F, G).

Figure S6

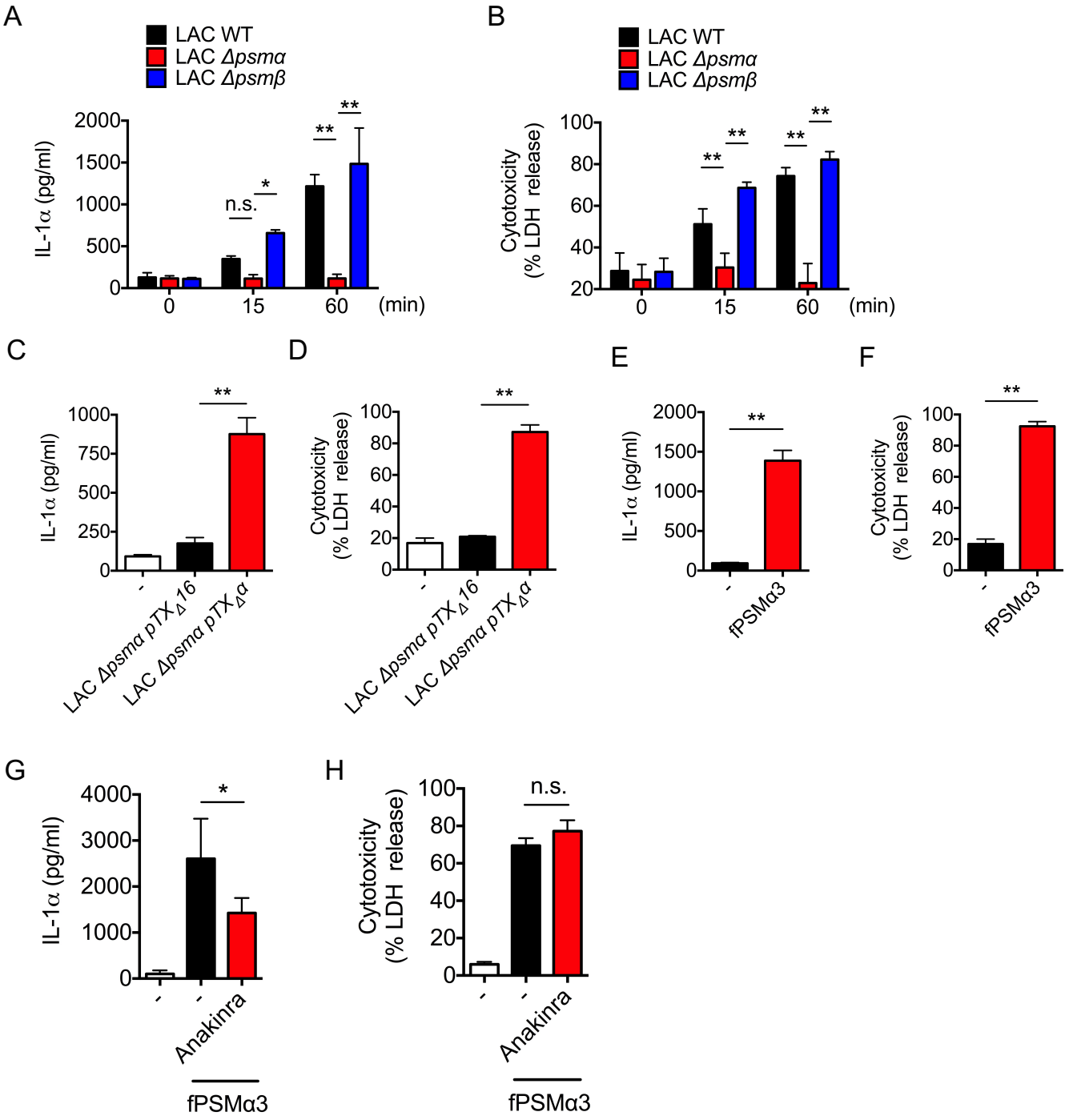

Figure S6. *S. aureus* PSMα peptides induce IL-1α release from human keratinocytes. Related to Figure 6.

A-B, IL-1α release (**A**) and cytotoxicity (**B**) of human primary KCs stimulated with culture supernatant of LAC WT, LAC Δ*psmα*, or LAC Δ*psmβ*. Data are representative of 3 independent experiments. **C-D,** IL-1α release (**C**) and cytotoxicity (**D**) of human primary KCs stimulated with culture supernatant of Δ*psmα S. aureus* reconstituted with *psmα* plasmid (LAC Δ*psmα* pTX$_{\Delta}$*α*) or its vector (LAC Δ*psmα* pTX$_{\Delta}$*16*). Data are representative of 2 independent experiments. **E-F**, IL-1α release (**E**) and cytotoxicity (**F**) of human primary KCs stimulated with synthetic formylated PSMα3 (fPSMα3). Data are representative of 2 independent experiments. **G-H,** IL-1α release (**G**), and cytotoxicity (**H**) of human primary KCs stimulated with formylated PSMα3 in the presence and absence of IL-1 receptor antagonist, anakinra. Data are representative of 2 independent experiments. n.s.; not significant, *P<0.05; **P<0.01, by Kruskal-Wallis test (A, B) or unpaired two-tailed Mann-Whitney U test (C-H).