Supplementary Data

Supplemental methods

Skin cell preparation and T cell isolation. For creating skin single cell suspensions, the epidermis dissociation kit (Miltenyi Biotec) was used to isolate epidermis from dermis after removing the subcutaneous fat. Epidermal single cell suspensions were then prepared according to the manufacturer's protocol. The remaining dermis was chopped into small pieces and was incubated in 300 μg/ml liberase and 50 U/ml DNase l (Merck) for 90 min to obtain single dermal cell suspensions. For T cell isolation, peripheral blood mononuclear cells (PBMCs) were collected from the peripheral blood of healthy controls and psoriasis patients by Ficoll-Paque (GE Healthcare) density gradient centrifugation. Splenocytes and dermal cells were collected from IMQ-mice or control mice. $CD4^+$ T cells were enriched with magnetic microbeads (BD Biosciences) and dermal γδ T cells were enriched with EasySep™ Mouse FITC Positive Selection Kit II (Stemcell). For Th1 and Th17 cells isolation, CD4 T cells were negatively selected by EasySep™ Human $CD4^+$ T Cell Enrichment Kit (Stemcell), then $CCR6^+$ or $CCR6^-$ cells were separated by EasySep™ Human FITC Positive Selection Kit II (Stemcell). Isolated cells were collected directly for subsequent experiments or cultured in RPMI 1640 medium (Gibco) with 10% fetal bovine serum (FBS, Gibco) at 37℃ and 5% CO_2.

Inhibitors treatment and retroviral transfection of T cells. For the GLS1 inhibition, BPTES (2 μM or indicated concentration; Selleckchem) or CB-839 (1 μM or indicated concentration; Selleckchem) were added to cultures of indicated polarizing Th subsets or primary $CD4^+$ T cells from psoriasis patients. In some experiments, sodium acetate (Sigma) was supplemented into cultures. For the MALT1 protease inhibition, MI-2 (0.5 μM or indicated concentration; Selleckchem) were added to cultures of polarizing Th17 cells or primary $CD4^+$ T cells from psoriasis patients. For the NF-κB inhibition, QNZ (20 nM; Selleckchem) were added to cultures of polarizing Th17 cells. For retroviral transduction, naïve $CD4^+$ T cells were cultured under non-polarizing condition for 24 h and spin transduced with concentrated retrovirus carrying hTRV-GLS1-GFP or hTRV-c-Jun-GFP and their control vector hTRV-NC-GFP (Hanbio Biotechnology) at 450×g for 90 min at 30 °C, respectively. After retroviral transfection, cells were cultured under Th17 polarizing condition for 3 days, and then were harvested for further analysis.

Flow Cytometry. For cell surface staining, cells were incubated with specific antibodies for 15 min on ice in the presence of anti-FcγR to block FcγR binding. For intracellular staining, cells were stimulated with 50 ng/ml phorbol 12-myristate 13-acetate (Sigma) and 1 μg/ml ionomycin (Sigma) in the presence of GolgiStop (BD Biosciences) for 4 h. After stimulation, cells were fixed and permeabilized with BD Cytofix/Cytoperm™ Plus (BD

Biosciences), followed by staining with fluorescent antibodies for an additional 30 minutes on ice in the dark. All samples were acquired with FACSVerse flow cytometer (BD Biosciences) and analyzed with FlowJo software (TreeStar). The following antibodies were used: PerCP-conjugated anti-human CD4 (BioLegend, 317431), Pacific blue-conjugated anti-human CD25 (BioLegend, 302620), FITC-conjugated anti-human CCR7 (BioLegend, 353215), APC-conjugated anti-human CD45RA (BioLegend, 304111), APC-conjugated anti-human IFN-γ (BioLegend, 502511), PE-conjugated anti-human IL-17A (BioLegend, 512305), PE-conjugated anti-human Foxp3 (BioLegend, 320007), APC-conjugated anti-mouse CD4 (BioLegend, 100411), PE-Cy7-conjugated anti-mouse IFN-γ (BioLegend, 505825), PE-conjugated anti-mouse IL-17A (BioLegend, 506903), FITC-conjugated anti-mouse IL-4 (Sungene Biotech, M100I9-02B), PE-conjugated anti-mouse Foxp3 (BioLegend, 320007).

Metabolic Assays. XF96 Extracellular Flux Analyzer (Seahorse Bioscience) was utilized for analyzing OCR according to manufacturer recommended protocols. In brief, cells were resuspended in the XF Base Medium containing 10 mM glucose (Sigma), 1 mM pyruvate (Sigma), 2 mM glutamine (Sigma), and planted in XF96 plate (2×10^5 cells/well) bounded with Cell-Tak (Corning). After centrifuged at 200×g (zero braking) for 2 minutes, cells were cultured in a CO_2-free incubator for 1 h before measurement. Real-time OCR was measured in response to 1 μM oligomycin, 0.25 μM fluorocarbonyl cyanide phenylhydrazone (FCCP), 0.5 μM rotenone and 0.5 μM antimycin A (Seahorse Bioscience) under basal conditions. SRC was defined as the percentage change in OCR between the initial basal readings and the injection of 0.25 μM of the FCCP to uncouple oxidative phosphorylation and electron transport.

Metabolites detection. Glutamate concentration was analyzed using a Glutamate Assay Kit (Sigma) following the manufacturer's instructions. In general, 1×10^6 cells were homogenized in the Glutamate Assay Buffer followed by centrifugation. The supernatants or serum were deproteinized with a 10 kDa MWCO spin filter prior to addition to the reaction. Total 50 μl samples were separated into a 96-well plate and 100 μl of the appropriate Reaction Mix was added to each of the wells. After incubating the reaction for 30 minutes at 37 °C in dark, the absorbance was measured at 450 nm. All samples and standards were run in duplicate.

Lactate concentration was analyzed using a Lactate Assay Kit (Sigma) following the manufacturer's instructions. In general, 1×10^6 cells were homogenized in the Lactate Assay Buffer followed by centrifugation. The supernatants were deproteinized with a 10 kDa MWCO spin filter prior to addition to the reaction. Total 50 μl samples were separated into a 96-well plate and 50 μl of the Master Reaction Mix was added to each of the wells. After incubating the reaction for 30 minutes at room temperature in dark, the absorbance was measured at 570 nm. All samples and standards were run in duplicate.

For measurement of cytosolic acetyl-CoA, 1×10^6 cells were lysed with lysis buffer (1% Triton X-100, 20 mM

Tris-HCl, pH=7.4, 150 mM NaCl) on ice for 10 min. The lysates were spun at 20, 000×g for 10 min at 4 °C, the pellets (nuclei and heavy membrane) were discarded, and the supernatants were used for acetyl-CoA measurement with an Acetyl-CoA Assay Kit (Abcam, ab87546).

GLS1 activity assay. GLS enzyme activity was measured by a Glutaminase Assay Kit (Biomedical Research Service Center, Buffalo, NY, USA) according to the manufacturer's instructions. In brief, 1×10^6 cells were homogenized and the supernatants were collected by centrifuging lysate. After diluting samples to 2 mg/ml, total 10 μl of each sample and 40 μl Glutamine solution or dH_2O (control well) were pipetted to a 96-well plate in duplicate and incubated in a humidified 37 ℃ incubator for 2 hours. The assay buffer was then added to the samples, followed by incubating for another 1 h at 37 °C. Reactions were terminated by adding 50 μl 3% Acetic acid to each well. The optical density (OD) at 492 nm was then measured using a microplate spectrophotometer. Each sample was analyzed in triplicate, and the enzyme activity was calculated following the manufacturer's instruction.

Immunobloting Analysis. Cells were collected and lysed using RIPA Lysis Buffer (Beyotime), complemented with complete EDTA-free protease inhibitor cocktail (Roche) and phosphatase inhibitor cocktail (Bimake). Lysates were incubated for 30 min on ice followed by centrifugation at 4 ℃ for 30 min at maximum speed. Supernatants were collected and protein contents were quantified with a BCA protein assay kit (Thermo Pierce). Cell total proteins (20-40 μg) were separated on 12% SDS-PAGE gels and transferred onto 0.22 μm PVDF membrane with the PowerPac wet-blot system (Bio-Rad). Membranes were incubated in blocking solution (5% BSA) and probed with primary antibodies to the following proteins: GLS1 (Sangon Biotech, D261715), MALT1 (CST, 2494), CYLD (CST, 4495), Bcl-10 (CST, 4237), c-Jun (CST, 9165), p-c-Jun (CST, 9164), p65 (CST, 8242), p-p65 (CST, 3033), c-Myc (CST, 5605), RORC (Abcam, ab80690), HK2 (CST, 2867), PKM2 (CST, 4053), LDHA (CST, 3582), OGDH (CST, 26865), MDH2 (CST, 11908), GLUD1 (Proteintech, 14299-1-AP), p-p70S6K (CST, 9208), p70S6K (CST, 9202), p-S6 (CST, 4858), S6 (CST, 2317) or β-actin (Sungene Biotech, km9001) at 4 ℃ for overnight. After six times washed in TBST for 1 h, the membranes were stained with secondary antibodies conjugated to HRP at a dilution of 1:3,000 (CST, goat anti-rabbit, 7074 or goat anti-mouse, 7076) at room temperature for 2 hours. Enhanced chemiluminescence (Millipore) was used to collect the chemiluminescence signals on Bio-Rad ChemiDoc MP Gel imaging system (Bio-Rad). Images were quantified by ImageJ analysis software.

Analysis of c-Jun stability. Vehicle or MI-2 (0.5 μM) treated human naive $CD4^+$ T cells were polarized into Th17 cells for 5 days. Cells were restimulated with anti-CD3 and CD28 for 2 h, followed by treating with 10 μg/mL cycloheximide (Sigma) for the indicated time points. Vehicle- or MI-2-treated polarizing Th17 cells were incubated with 5 μM MG-132 (Selleckchem) or not for 12 h. Cells were harvested and subjected to immunoblotting.

Immunohistochemistry. Skin sections (5 μm) were deparaffinized, boiled in antigen retrieval solution (10 mM sodium citrate, 0,05% Tween 20, pH6), and incubated with rabbit anti-GLS1 antibody at 4℃ overnight. Sections were rinsed with PBS and incubated with goat anti-rabbit antibody for 1h. Slides were developed with DAB substrate (Dako) and then counterstained with Mayers hematoxylin. Integrated optical density of GLS1 staining was quantified for mean gray value in the epidermal layer with ImageJ software.

Confocal microscopy. Cells were washed with PBS and fixed for 15 min at room temperature with 4% (vol/vol) paraformaldehyde. After quenching PFA with 50 mM NH_4Cl for 15 min, cells were washed with PBS and permeabilized in blocking buffer (0.02% Triton X-100 and 5% BSA in PBS) for 1 h. Then cells were incubated for 4 h with rabbit anti-GLS1 antibodies. After three washes with PBS, the cells were incubated for another 2 h with Alexa Fluor 488–conjugated anti–rabbit IgG (CST, 4412). Subsequently, the cells were washed three times with PBS and were mounted with Vectashield mounting medium containing DAPI (Abcam). All images were collected with a Leica TCS SP2 AOBS confocal laser scanning microscope (Leica).

ChIP-seq. The library was prepared with KAPA library preparation kit (Kapa Biosystems) and sequenced using a HiSeq 2000 platform (Illumina). Reads were first trimmed using Trimmomatic (v0.33). Reads were trimmed if first/last 3 nucleotides had phread quality score of < 15 or at the point where a sliding window of 4 nucleotides averaged a phred quality score < 15. Illumina adapters were also removed. The reads were then aligned using bowtie2 (v2.2.6, options–fr--no-discordant). Multimapping reads were removed after alignment. Peak calling was done using MACS2 (v2.1.0) on pooled replicates and individual samples using *p* value cutoff of 0.01. The peaks were then filtered further using IDR to make sure the peaks are consistent among replicates. The promoter was annotated as region within 2,000 bp from TSS, intron was annotated as region within the gene body but not in the promoter region, and peaks at regions outside but close to gene body were annotated as intergenic.

Enzyme linked immunosorbent assay (ELISA). Supernatant culture medium or serum was collected, the amounts of IL-17A or IFN-γ were measured by ELISA kits, following the manufacturer's instructions (Biolegend).

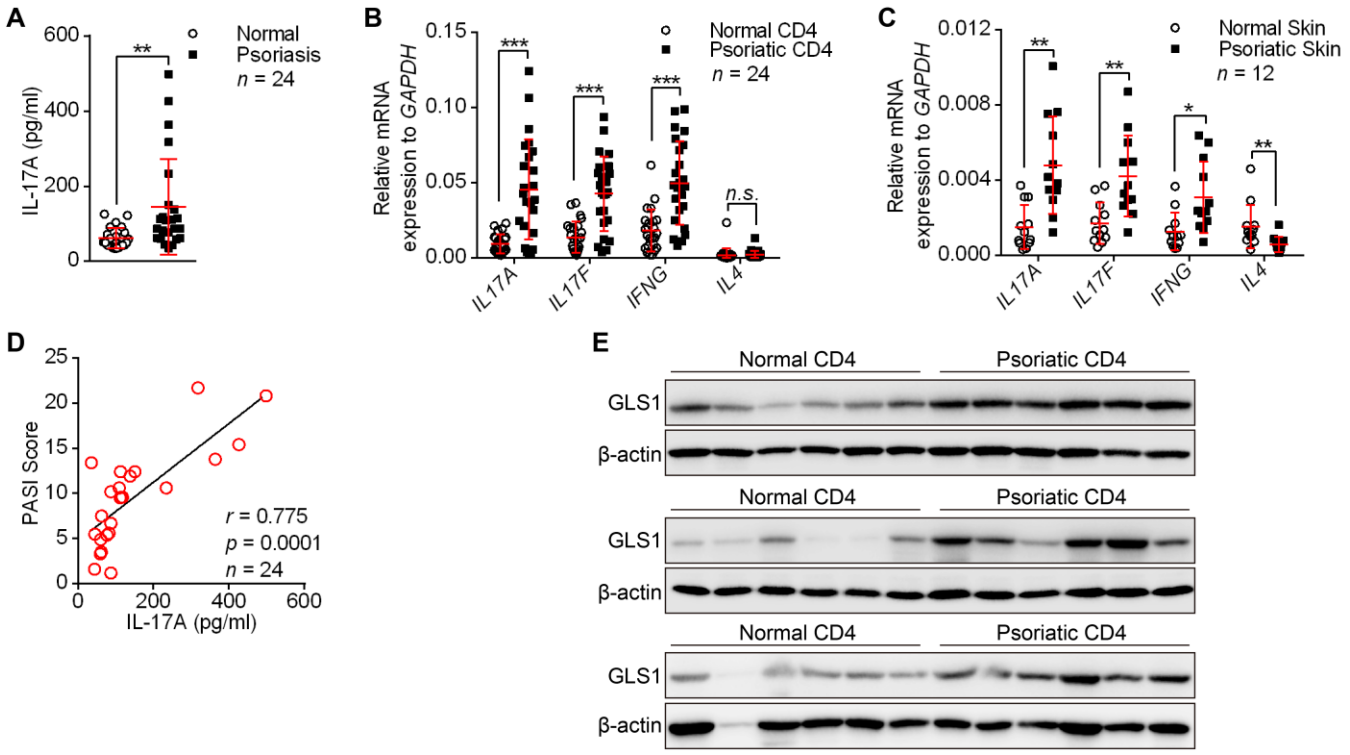
Keratinocyte culture and transfection. HaCaT cells (CLS Cell Lines Service, 300493, Germany) were cultured in DMEM (Gibco, USA) with 10% FBS (Gibco, USA) at 37°C, 5% CO_2. Cells at passage 2-6 were used for subsequent experiments. For transfection, HaCaT were seeded in 6-well plate with 2 ml culture medium, following 50 μl retrovirus carrying hTRV-GLS1-GFP or control vector hTRV-NC-GFP (Hanbio Biotechnology) were added into the medium. After 24 h incubation, the medium was replaced by fresh culture medium. For siRNA, HaCaT were seeded in 6-well plate with 2 ml serum-free basal medium one day before transfection. Then the mixture of si-c-Jun (CST, 6203) or its corresponding control (CST, 6568) with Lipofectamine 3000 (Invitrogen) were added into the medium at 200 nM. After 8 h incubation, the medium was replaced by fresh culture medium. The cells

were further cultured for 24 h or 48 h and then collected for the subsequent experiments.

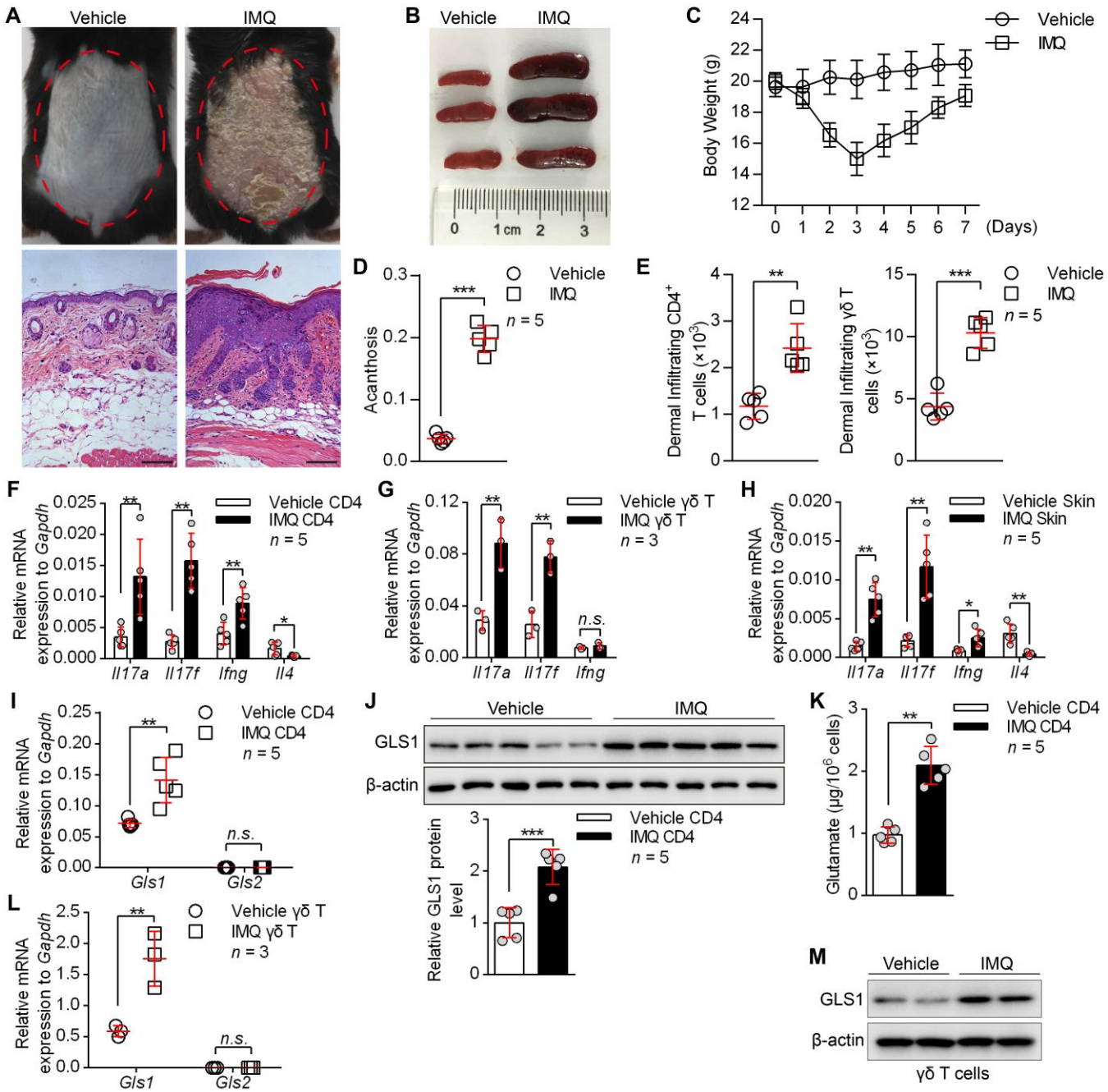
CCK8 assay. HaCaT were seeded in 96-well plates in triplicates followed by indicated treatment for 24 h or 48 h. The Cell Counting Kit-8 (CCK8, Beyotime) was used to evaluate cell proliferation. Briefly, 10 μl CCK8 solution was added to each well, and cells were incubated for 3 h at 37℃, 5% CO_2. Cell viability was detected at 450 nm.

Cell chemotaxis assay. Transwell assays (pore size 5.0 μm, Corning, USA) were performed to assess the chemotaxis of keratinocytes to $CD4^+$ T cells. Human $CD4^+$ T cells (5×10^5) were seeded into the upper chambers in 200 μl serum-free RPMI 1640 (Gibco) medium. Then 500 μl culture supernatants collected from HaCaT cells transfected with hTRV-GLS1/hTRV-NC or treated with BPTES/CB-839 was added to the lower chambers respectively as a chemotactic factor. Following a 2 h incubation in 37°C, 5% CO_2, the non-migrated cells on the upper surface of the filter were carefully removed with a cotton swab. Cells that migrated through the 5.0 μm sized pores and adhered to the lower surface of the filter were fixed with 90% ethanol for 15 min and then were stained with 0.1% crystal violet followed by washing with deionized water. Cells in five non-overlapped fields were counted under a microscope and the mean cell counts were calculated.

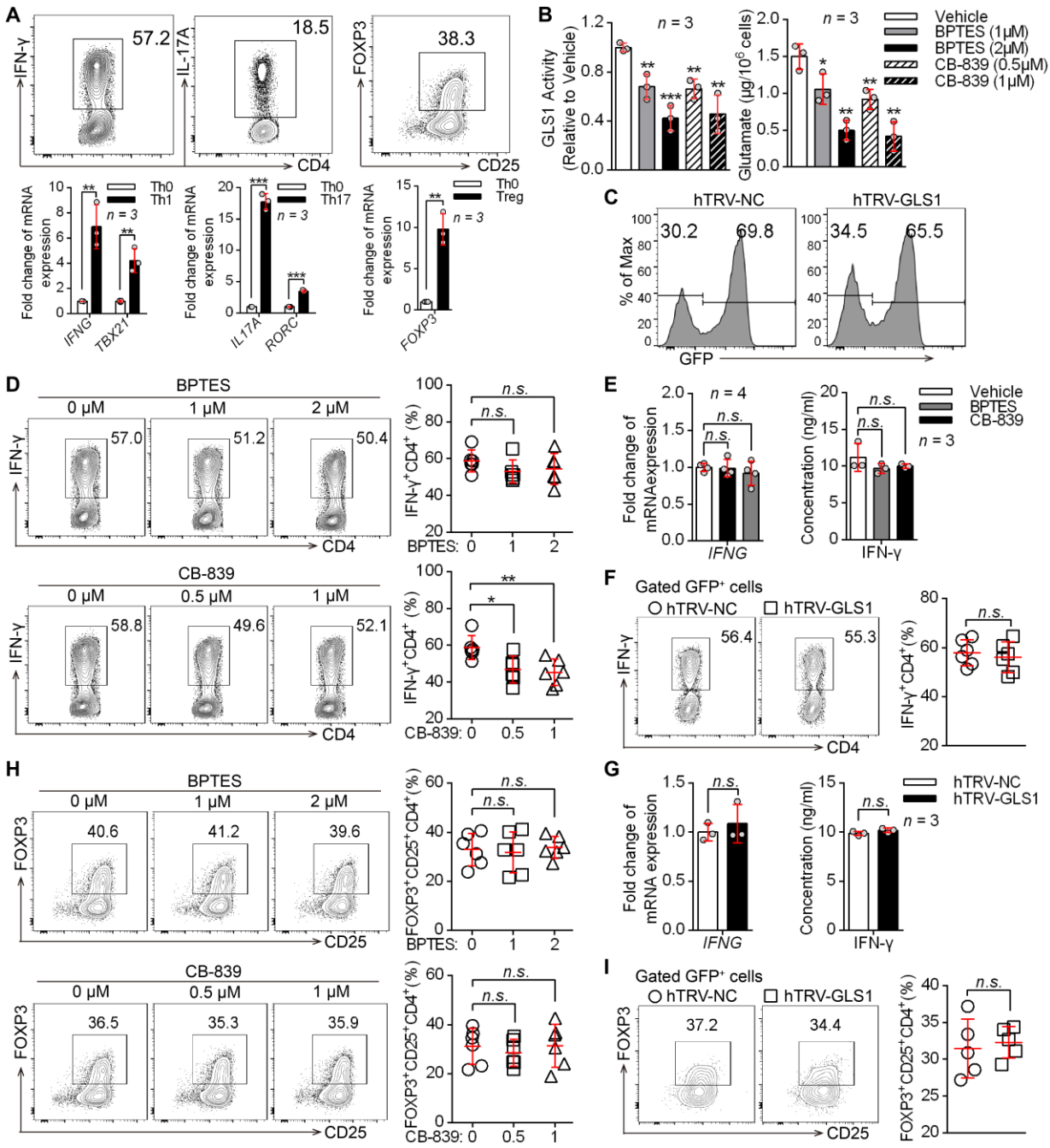
Supplemental Figures



Supplemental Figure 1. Abnormal cytokine and GLS1 expression in psoriatic CD4$^+$ T cells or skin lesions. (A) IL-17A concentration in serum from healthy controls and psoriasis patients (n = 24). (**B** and **C**) The relative mRNA expression of *IL17A, IL17F, IFNG* and *IL4* in CD4$^+$ T cells (**B**, n = 24) and skin (**C**, n = 12) from healthy controls and psoriasis patients. (**D**) Correlation of IL-17A concentration with PASI scores in psoriasis patients (n = 24). (**E**) The protein expression of GLS1 in CD4$^+$ T cells derived from PBMC of healthy controls and psoriasis patients. Samples from 18 individuals of total 24 were shown. Data are presented as mean ± SD. Two-tailed unpaired Student's t test (**A-C**) or Spearman's r test (**D**) was used to determine statistical significance (*P < 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).



Supplemental Figure 2. Vigorous GLS1-mediated glutaminolysis in splenic CD4⁺ T cells from IMQ-induced psoriasis-like mice. C57BL/6 mice were painted on the shaved back skin with IMQ cream or not for 7 consecutive days. (**A-E**) The clinical manifestations and H&E staining of dorsal skin (**A**, scale bar: 100 μm), splenomegaly (**B**), body weight (**C**), acanthosis (**D**) and dermal infiltrating CD4⁺ and γδ T cells (**E**) (n = 5). (**F-H**) The relative mRNA expression of *Il17a*, *Il17f*, *Ifng* and *Il4* in CD4⁺ T cells (**F,** n = 5), γδ T cells (**G,** n = 3) and skin (**H,** n = 5). (**I** and **J**) The relative mRNA (**I,** n = 5) and protein (**J**) expression of GLS1 or GLS2 in splenic CD4⁺ T cells. (**K**) Glutamate concentration in CD4⁺ T cells from vehicle- and IMQ-mice (n = 5). (**L** and **M**) The relative mRNA (**L**, n = 3) and protein (**M**) expression of GLS1 or GLS2 in dermal γδ T cells. Data are presented as mean ± SD and represent one of three independent experiments with consistent results. Two-tailed unpaired Student's t test (**D-L**) was used to determine statistical significance (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, *n.s.*, not significant).



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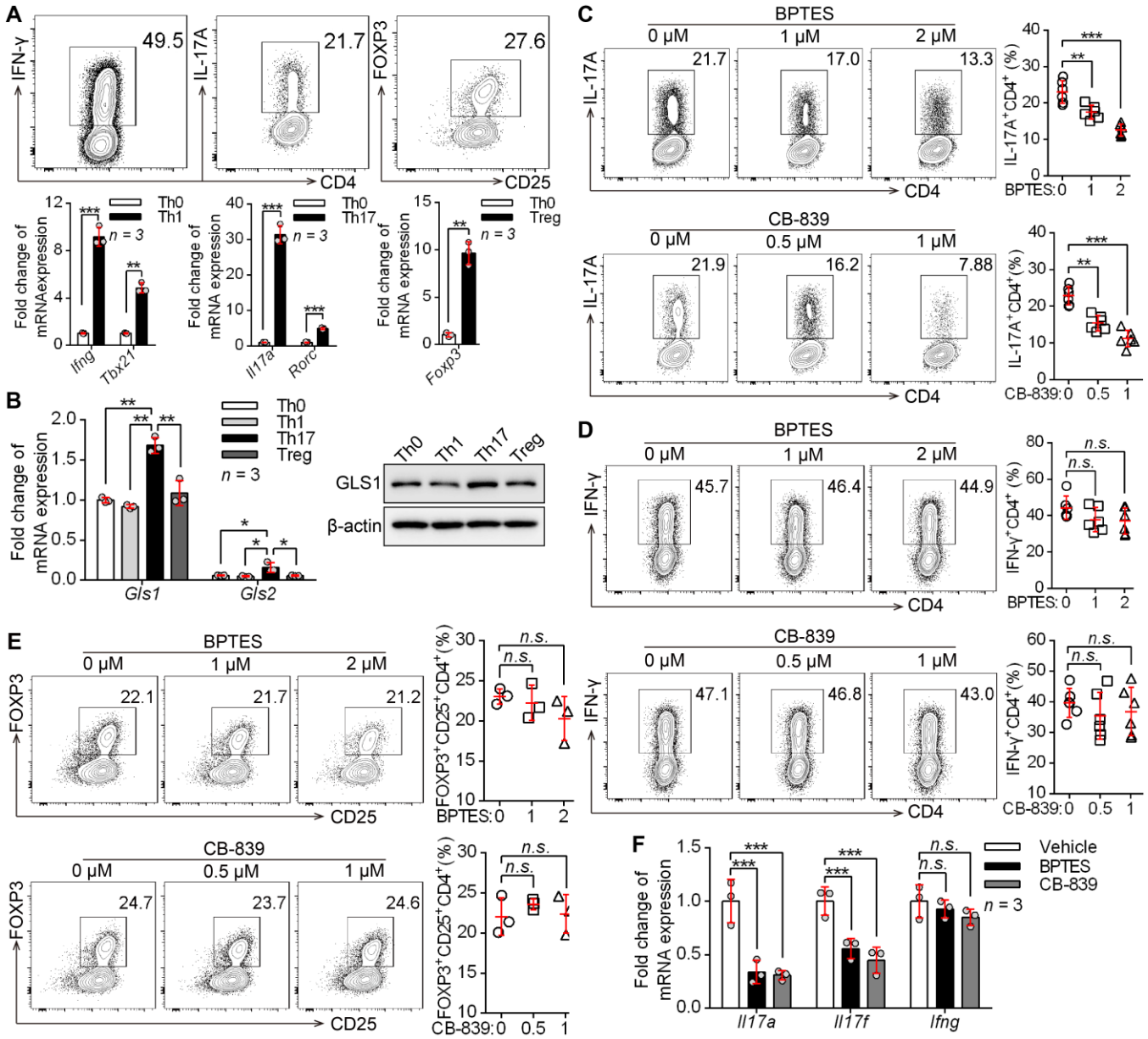
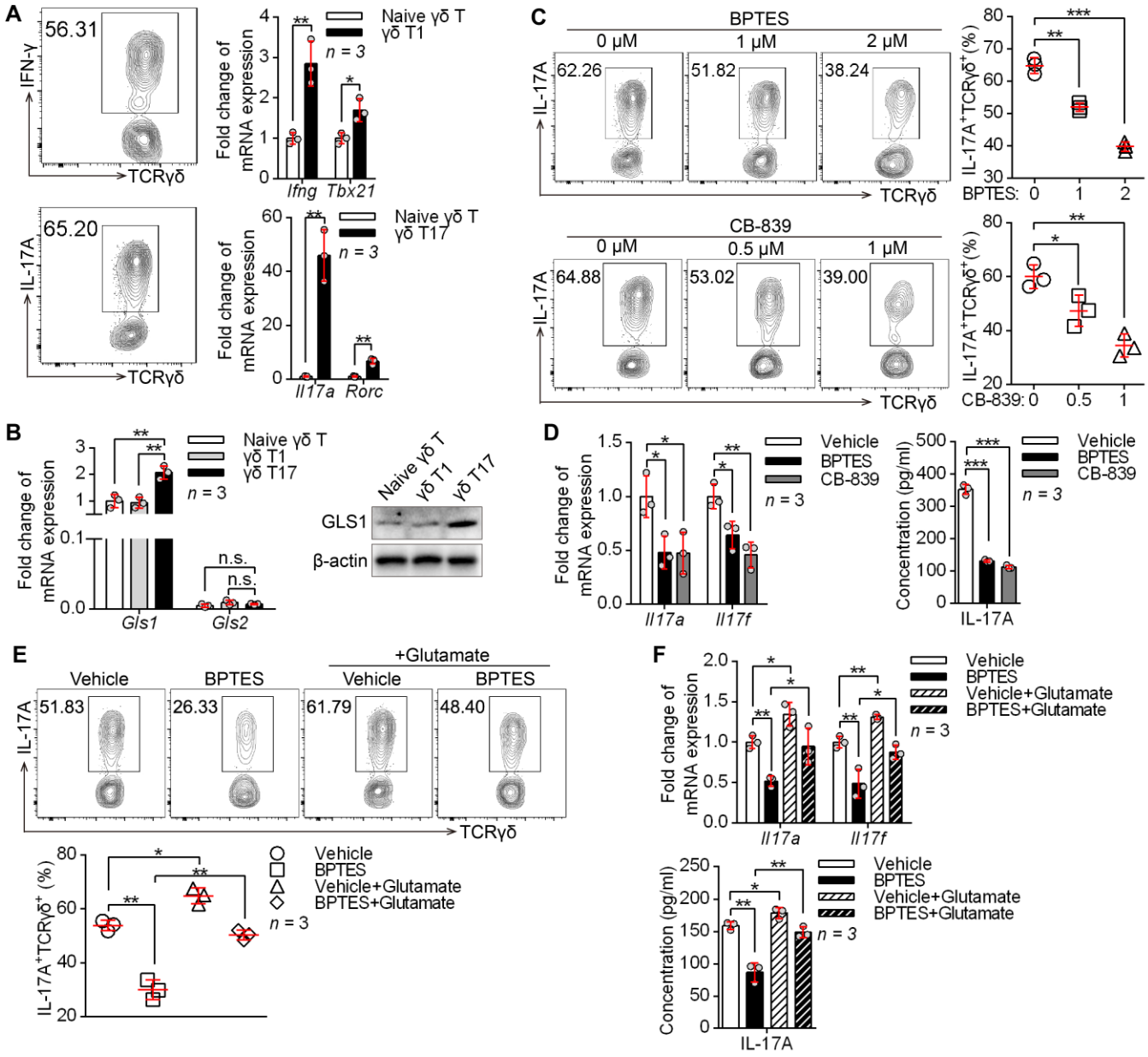
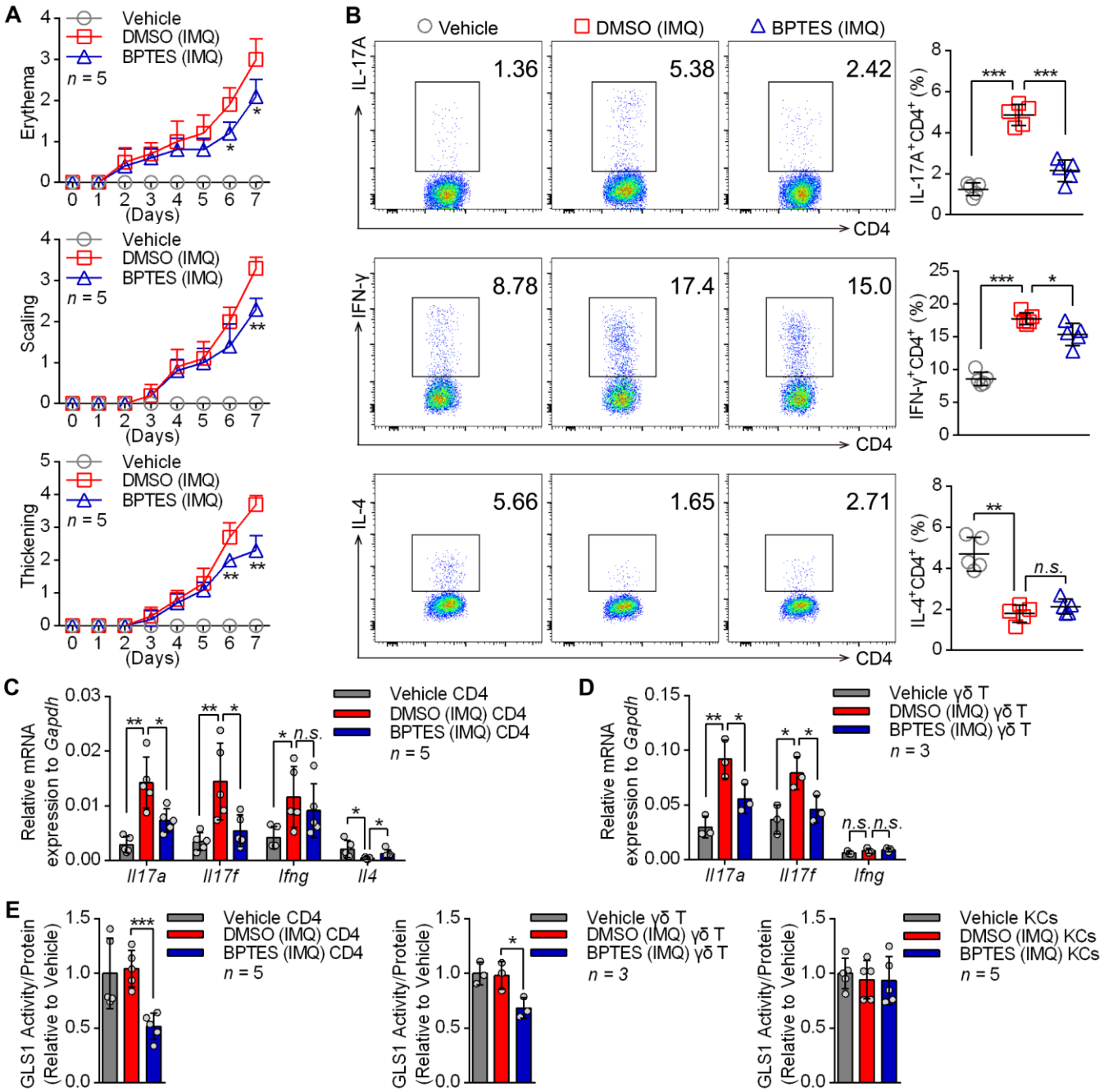
199 **Supplemental Figure 3. In vitro differentiation of human naïve CD4⁺ T cells.** (**A**) Human naïve CD4⁺ T cells
200 were polarized under indicated conditions in vitro for 5 days. Flow cytometry for the percentages of Th1, Th17 and
201 iTreg cells (upper panel). q-PCR for the mRNA levels of corresponding specific cytokines and transcription factors
202 in Th0 cells and polarized Th cells (lower panel, n = 3). (**B**) GLS1 activity and glutamate concentration in human
203 Th17-polarizing cells treated with BPTES or CB-839 for 5 days (n = 3). (**C**) Transfection efficiency (GFP⁺ cells) of
204 hTRV-NC or hTRV-GLS1 in human Th17-polarizing cells. (**D-I**) Human naïve CD4⁺ T cells were polarized into
205 Th1 or iTreg cells for 5 days under indicated treatments. (**D** and **F**) Flow cytometry for the percentage of Th1 cells.
206 Statistical analysis data are shown in the right panel (n = 6). (**E** and **G**) The relative mRNA expression and protein
207 levels of IFN-γ (n = 3). (**H** and **I**) Flow cytometry for the percentage of iTreg cells. Statistical analysis data are
208 shown in the right panel (n = 6 or 5). Data are presented as mean ± SD and represent one of at least two
209 independent experiments with consistent results. Two-tailed unpaired Student's t test (**A**, **F**, **G, I**) or one-way
210 ANOVA with Tukey's multiple comparisons test (**B**, **D**, **E, H**) was used to determine statistical significance (*P <
211 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).



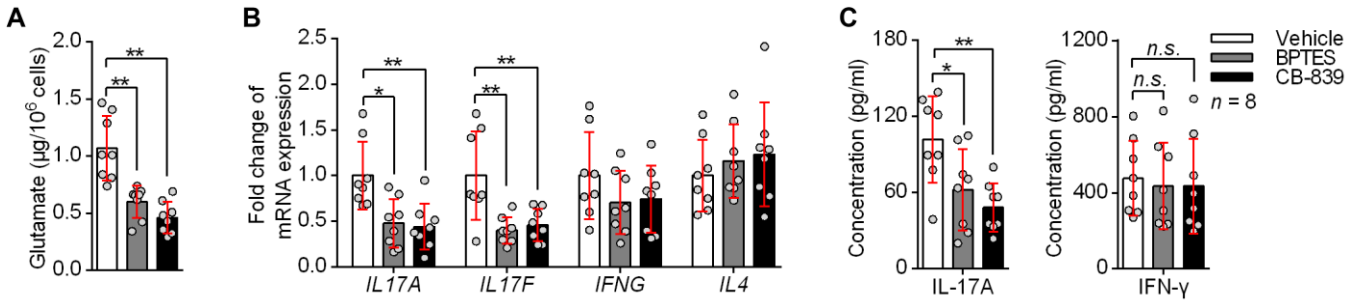
Supplemental Figure 4. GLS1-mediated glutaminolysis regulates Th cell differentiation in mice. (**A** and **B**) Naïve CD4$^+$ T cells from mouse spleen were polarized under indicated conditions in vitro for 5 days. Flow cytometry for the percentages of Th1, Th17 and iTreg cells (upper panel). q-PCR for the mRNA levels of corresponding specific cytokines and transcription factors in Th0 cells and polarized Th cells (lower panel) (**A**, n = 3). The relative mRNA and protein expressions of GLS1 or GLS2 (**B**, n = 3). (**C-F**) Naïve CD4$^+$ T cells from mouse spleen were either left untreated or treated with BPTES or CB-839 and polarized under indicated conditions in vitro for 5 days. Flow cytometry for the percentage of Th17 (**C**), Th1 (**D**) and iTreg (**E**) cells. Statistical analysis data are shown in the right panel (n = 6 or 3). (**F**) q-PCR for the mRNA levels of corresponding specific cytokines in polarized Th cells (n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t test (**A**) or one-way ANOVA with Tukey's multiple comparisons test (**B-F**) was used to determine statistical significance (*P < 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).



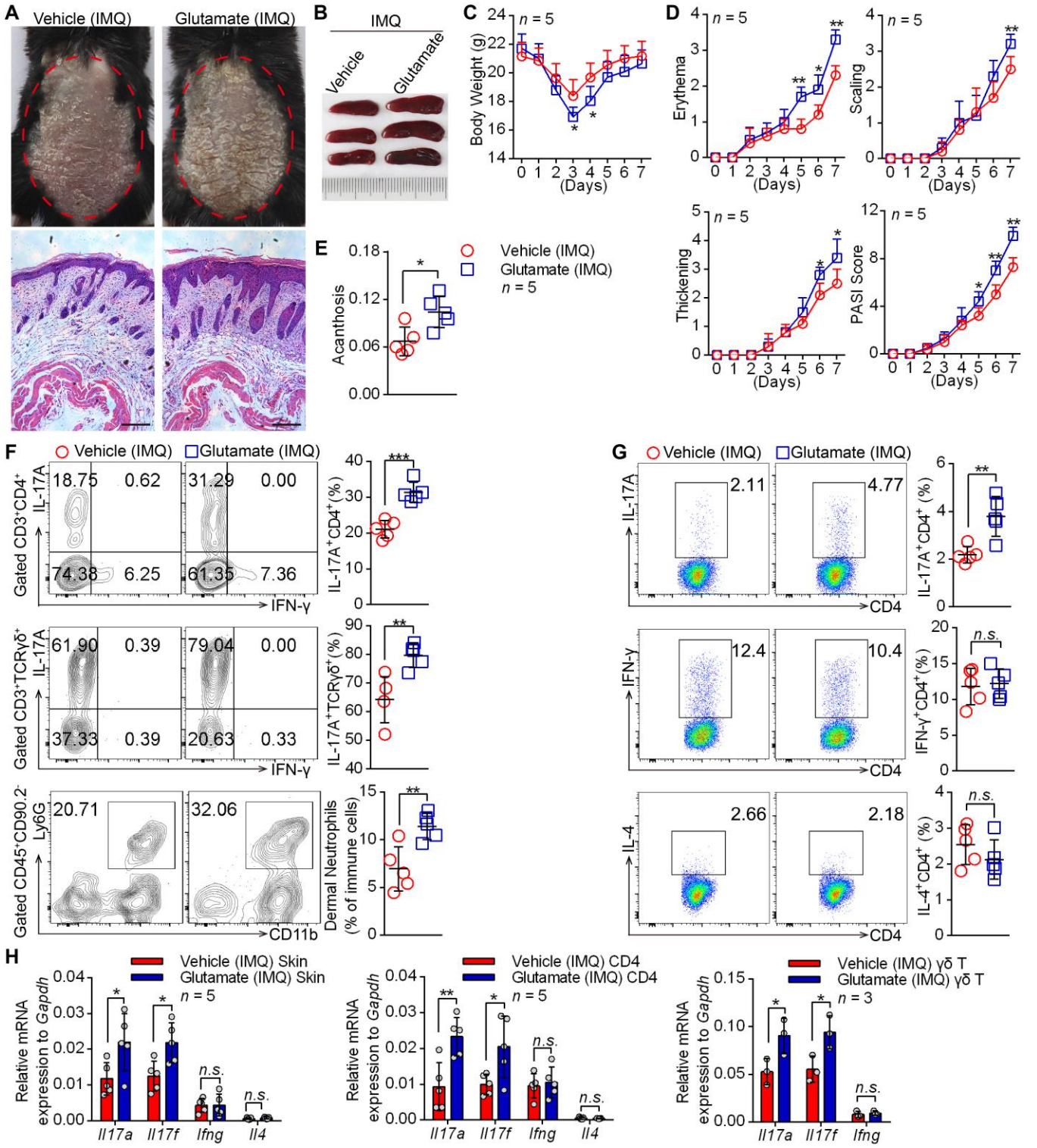
Supplemental Figure 5. GLS1-mediated glutaminolysis regulates γδ T17 cell differentiation in mice. (**A** and **B**) Naïve γδ T cells were polarized under indicated conditions in vitro for 10 days. Flow cytometry for the percentages of polarized γδ T1 and γδ T17 cells (upper panel). q-PCR for the mRNA levels of corresponding specific cytokines and transcription factors in naïve γδ T cells and polarized cells (lower panel) (**A**, n = 3). The relative mRNA and protein expressions of GLS1 or GLS2 (**B**, n = 3). (**C** and **D**) Naïve γδ T cells were either left untreated or treated with BPTES or CB-839 and polarized into γδ T17 cells for 10 days in vitro. Flow cytometry for the percentage of γδ T17 cells. Statistical analysis data are shown in the right panel (**C**, n = 3). The relative mRNA expression and protein levels of IL-17A or IL-17F (**D**, n = 3). (**E** and **F**) Naïve γδ T cells were treated with vehicle or BPTES and polarized into γδ T17 cells for 5 days, following either left untreated or supplemented with glutamate for another 5 days. Flow cytometry for the percentage of γδ T17 cells. Statistical analysis data are shown in the lower panel (**E**, n = 3). The relative mRNA expression and protein levels of IL-17A or IL-17F (**F**, n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t-test (**A**) or One-way ANOVA with Tukey's multiple comparisons test (**B-F**) was used to determine statistical significance (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).



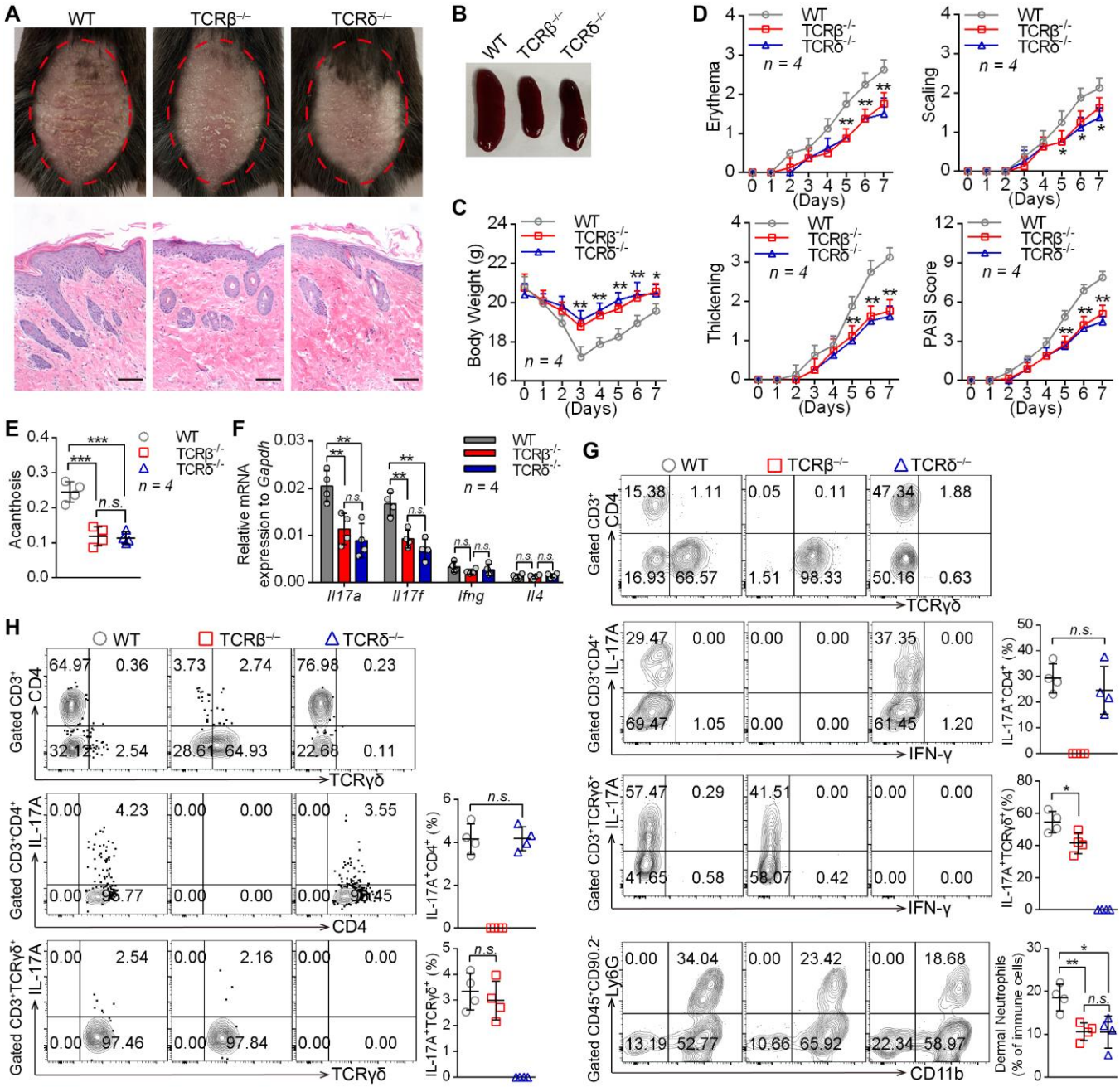
Supplemental Figure 6. Administration of GLS1 inhibitor ameliorates T cell-mediated skin inflammation in the IMQ-induced psoriasis-like mice. (**A**) The individual parameters of PASI score in **Figure 3** (n = 5). (**B**) The percentage of Th17, Th1 and Th2 cells in splenic $CD4^+$ T cells from mice in **Figure 3**. Statistical data are shown in the right panel (n = 5). (**C** and **D**) The relative mRNA expression of *Il17a*, *Il17f*, *Ifng* and *Il4* in splenic $CD4^+$ T cells (**C**, n = 5) or dermal γδ T cells (**D**, n = 3) from mice in **Figure 3**. (**E**) The ratio of GLS1 activity to GLS1 protein in splenic $CD4^+$ T cells (n = 5), dermal γδ T cells (n = 3) and keratinocytes (n = 5) from mice in **Figure 3**. Data are presented as mean ± SD and represent one of three independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test was used to determine statistical significance (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, *n.s.*, not significant).



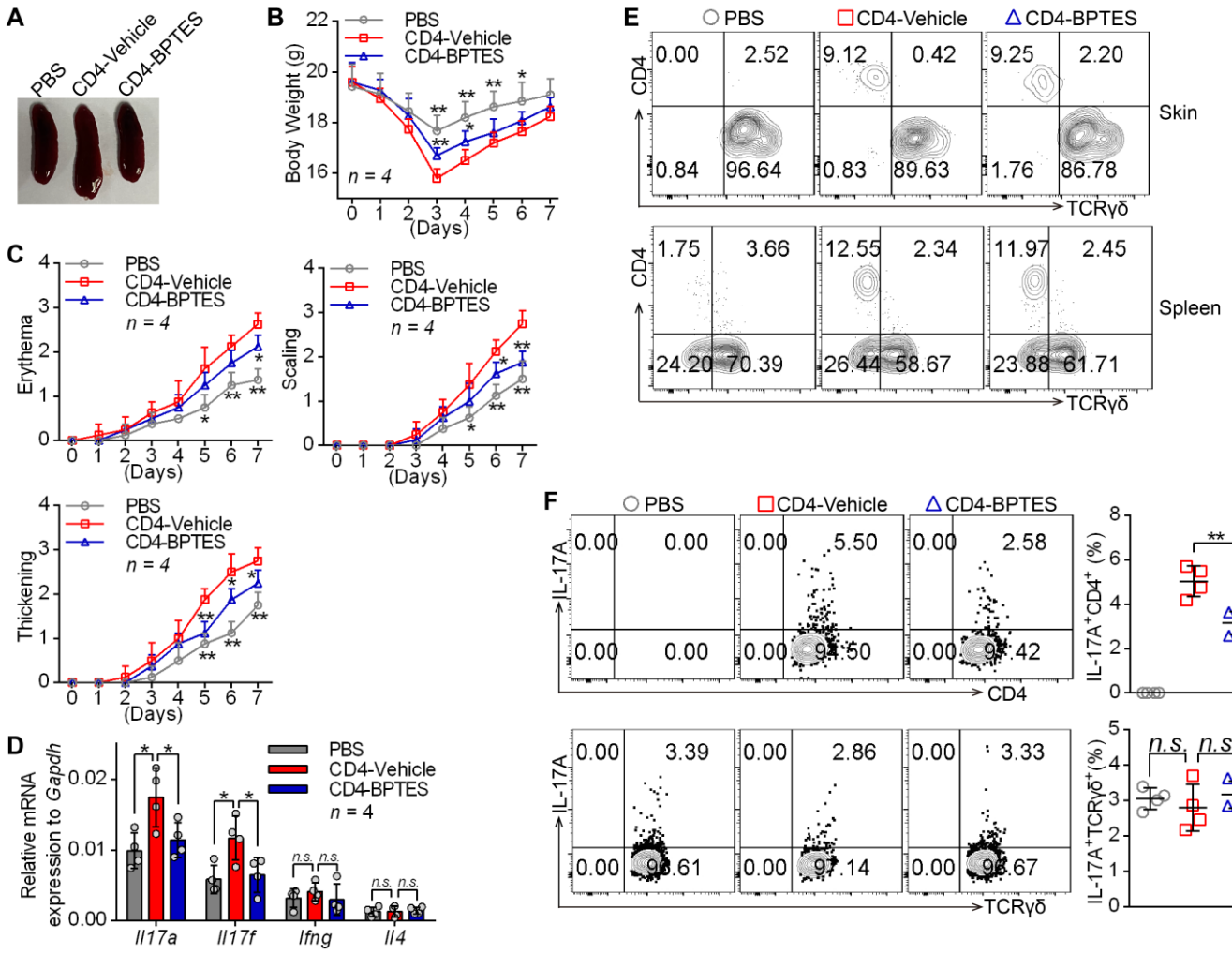
Supplemental Figure 7. Administration of GLS1 inhibitor decreased pro-inflammation cytokines in human psoriatic CD4⁺ T cells. (**A-C**) Human psoriatic CD4⁺ T cells were either left untreated or treated with BPTES or CB-839 for 48h (n = 8). Cellular glutamate concentration (A). q-PCR for the relative mRNA expression of *IL17A, IL17F, IFNG* and *IL4* (B). ELISA for supernatant protein level of IL-17A and IFN-γ (C). Data are represented as mean ± SD. One-way ANOVA with Tukey's multiple comparisons test was used to determine statistical significance (*$P < 0.05$, **$P < 0.01$, *n.s.*, not significant).



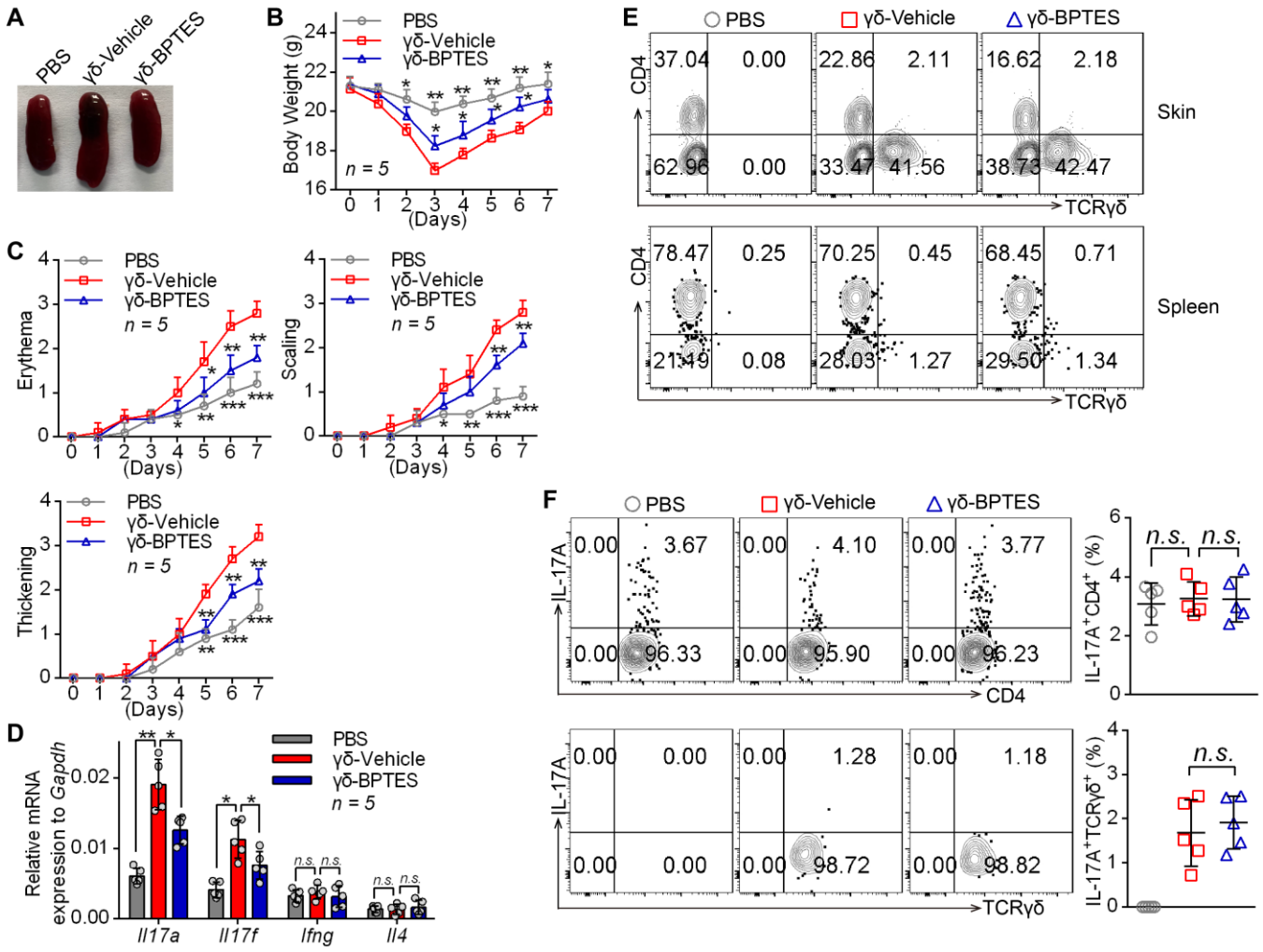
Supplemental Figure 8. Glutamate accelerates the development of psoriasis. C57BL/6 mice were treated with 2% glutamate or water by gavage (400 μl/mice/day) during the application of IMQ for 7 consecutive days. (**A-E**) The clinical manifestations and H&E staining of the back skin (**A**, scale bars: 200 μm), splenomegaly (**B**), body weight (**C**), PASI score (**D**) and acanthosis (**E**) (n = 5). (**F and G**) The percentage of IL-17A$^+$ in dermal CD4 and γδ T cells, neutrophils in dermal CD45$^+$ lymphocytes (**F**), and Th17, Th1 and Th2 in splenic CD4 T cells (**G**). Statistical data are shown in the right panel (n = 5). (**H**) The relative mRNA expression of *Il17a, Il17f, Ifng* and *Il4* in skin (n = 5), splenic CD4$^+$ T cells (n = 5) or dermal γδ T cells (n = 3). Data are presented as mean ± SD and represent one of three independent experiments with consistent results. Two-tailed unpaired Student's t test (**C-H**) was used to determine statistical significance (*P < 0.05, **P < 0.01, *n.s.*, not significant).



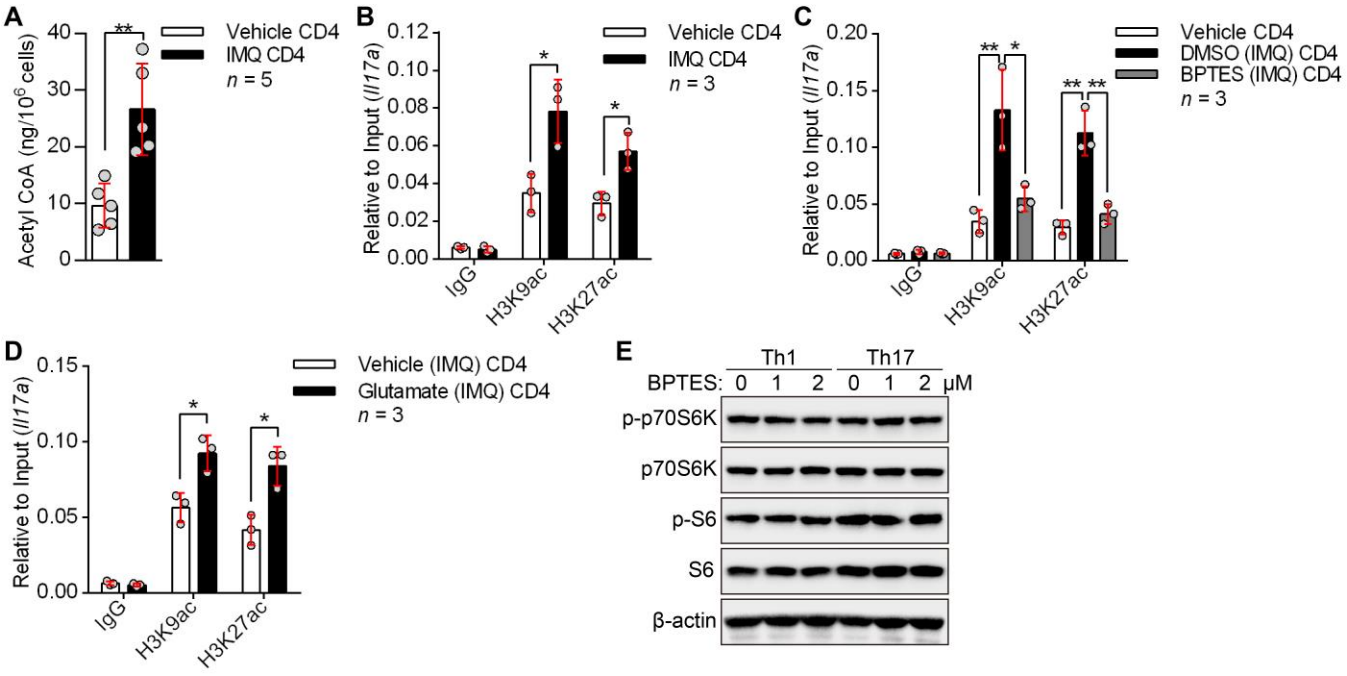
Supplemental Figure 9. Both αβ T cells and γδ T cells were critical in the pathological phenotype of IMQ-induced psoriasis-like mice. WT, *Tcrb*$^{-/-}$ and *Tcrd*$^{-/-}$ mice were treated with IMQ cream to induce psoriasis. Representative phenotypic presentation and H&E staining of skin lesions (**A**, scale bar: 100 μm), splenomegaly (**B**), body weight (**C**), PASI score (**D**), and acanthosis (**E**) (n = 4). (**F**) The relative mRNA expression of *Il17a*, *Il17f*, *Ifng* and *Il4* in skin lesions (n = 4). (**G** and **H**) The percentage of IL-17A$^+$ in dermal CD4 and γδ T cells, neutrophils in dermal CD45$^+$ lymphocytes (**G**), and IL-17A$^+$ in splenic CD4 and γδ T cells cells (**H**). Statistical analysis data are shown in the right panel (n = 4). Data are presented as mean ± SD and represent one of three independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test (**C**-**H**) was used to determine statistical significance (*P < 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).



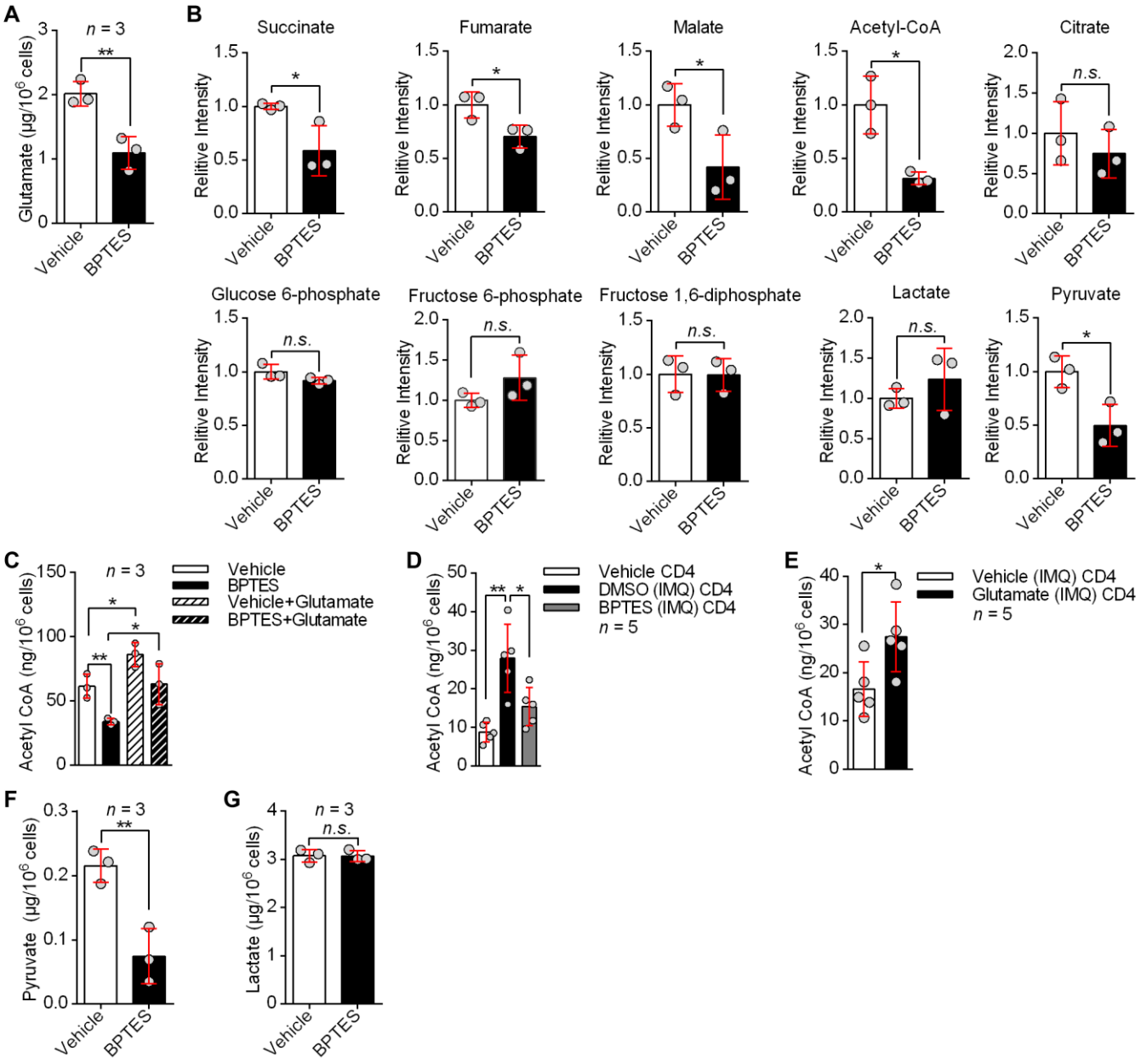
Supplemental Figure 10. Effects of GLS1-mediated glutaminolysis in CD4$^+$ T cells on IMQ-induced psoriasis-like skin inflammation. (**A-C**) Splenomegaly(**A**), body weight (**B**), and the individual parameters of PASI score (**C**) in **Figure 4A** (n = 4). (**D**) The relative mRNA expression of *Il17a*, *Il17f*, *Ifng* and *Il4* in skin lesions in **Figure 4A** (n = 4). (**E** and **F**) Detection of transferred CD4$^+$ T cells in skin and spleen (**E**), the percentage of IL-17A$^+$ in splenic CD4 and γδ T cells (**F**) from the recipient *Tcrb*$^{-/-}$ mice in **Figure 4A**. Statistical analysis data are shown in the right panel (n = 4). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test was used to determine statistical significance (*P < 0.05, **P < 0.01, *n.s.*, not significant).



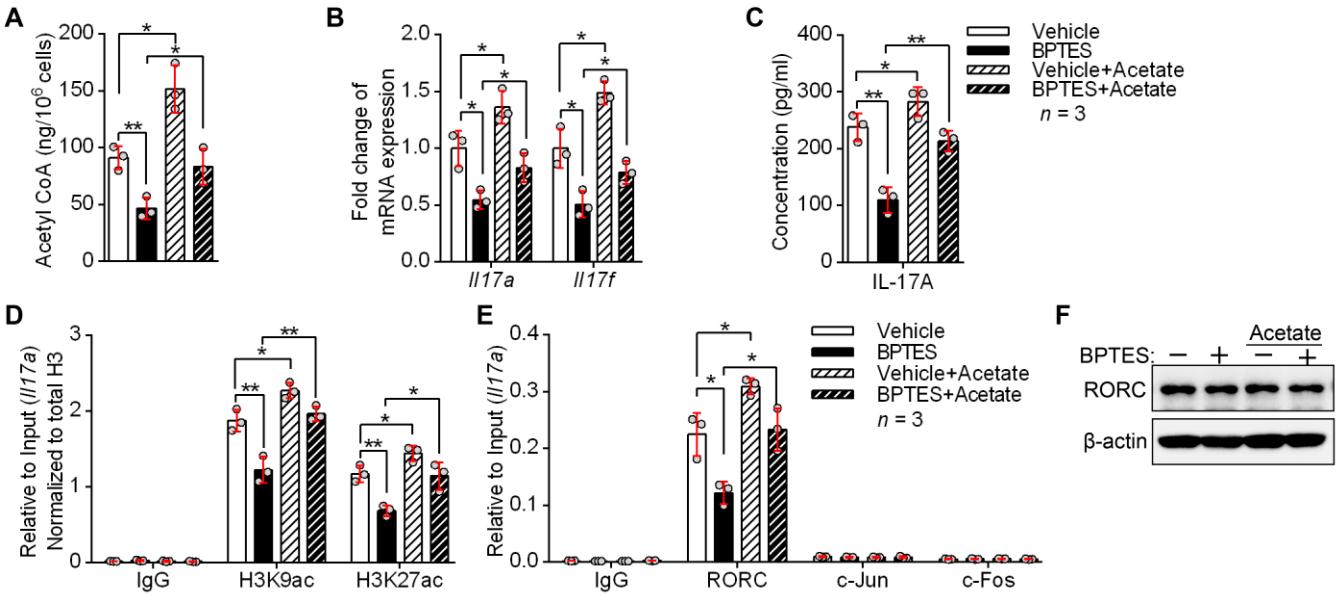
Supplemental Figure 11. Effects of GLS1-mediated glutaminolysis in γδ T cells on IMQ-induced psoriasis-like skin inflammation. (**A-C**) Splenomegaly(**A**), body weight (**B**), and the individual parameters of PASI score (**C**) in **Figure 4E** (n = 5). (**D**) The relative mRNA expression of *Il17a*, *Il17f*, *Ifng* and *Il4* in skin lesions in **Figure 4E** (n = 5). (**E** and **F**) Detection of transferred γδ T cells in skin and spleen (**E**), the percentage of IL-17A$^+$ in splenic CD4 and γδ T cells (**F**) from the recipient *Tcrd*$^{-/-}$ mice in **Figure 4E**. Statistical analysis data are shown in the right panel (n = 5). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test was used to determine statistical significance (*P < 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).



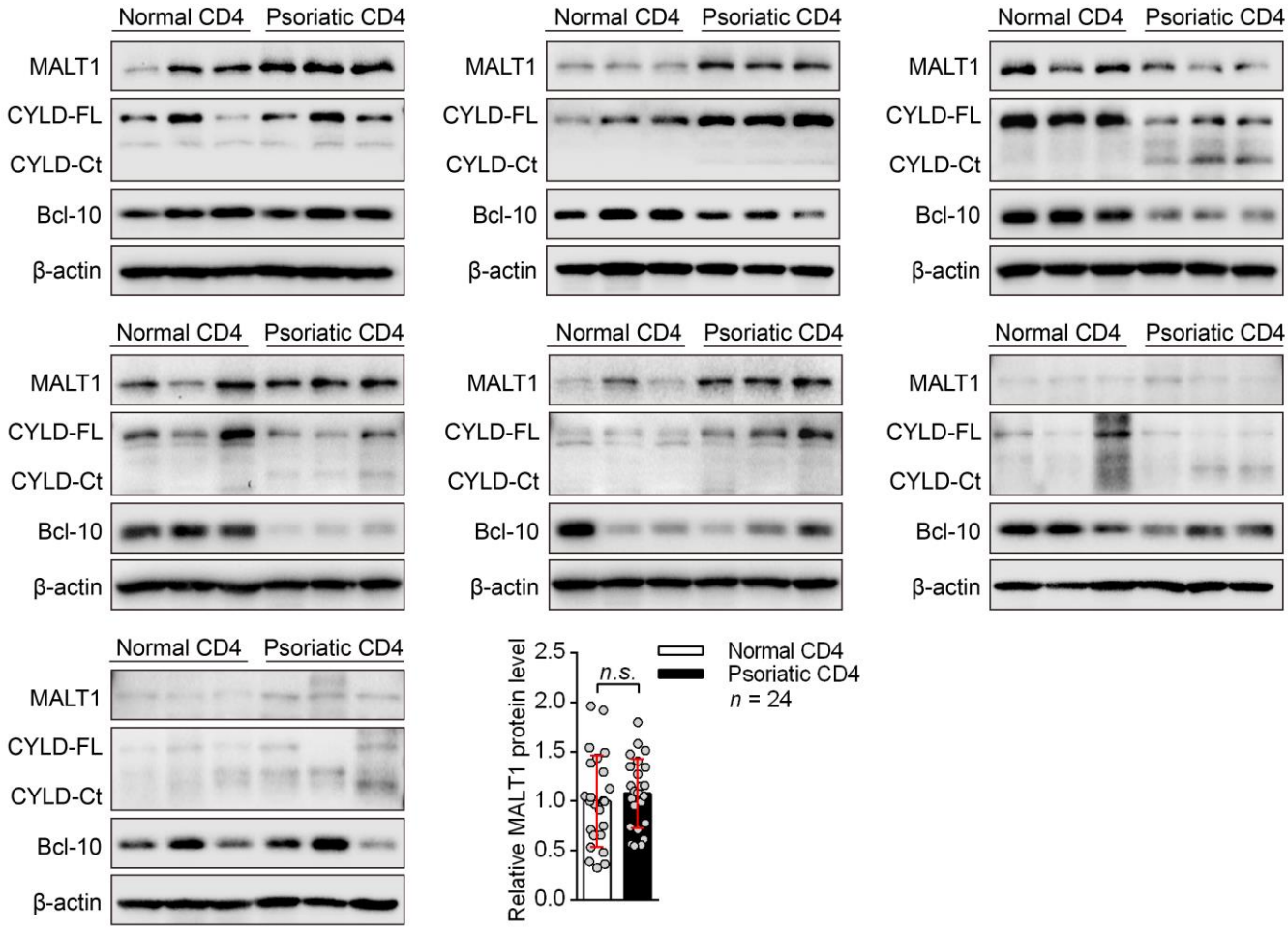
Supplemental Figure 12. Effects of GLS1-mediated glutaminolysis on histone acetylation of *Il17a* promoter regions. (**A** and **B**) Acetyl-CoA concentration (**A**, n = 5) and histone acetylation of *Il17a* promoter regions (**B**, n = 3) in CD4$^+$ T cells from vehicle- and IMQ-mice. (**C** and **D**) Histone acetylation of *Il17a* promoter regions in CD4$^+$ T cells from mice in **Figure 3** (**C**, n = 3) and **Supplemental Figure 8** (**D**, n = 3). (**E**) Human naïve CD4$^+$ T cells were either left untreated or treated with BPTES and polarized into Th1 and Th17 cells for 5 days. Representative blots for mTORC1 signaling pathway. Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t test (**A**, **B**, **D**) or one-way ANOVA with Tukey's multiple comparisons test (**C**) was used to determine statistical significance (*P < 0.05, **P < 0.01).



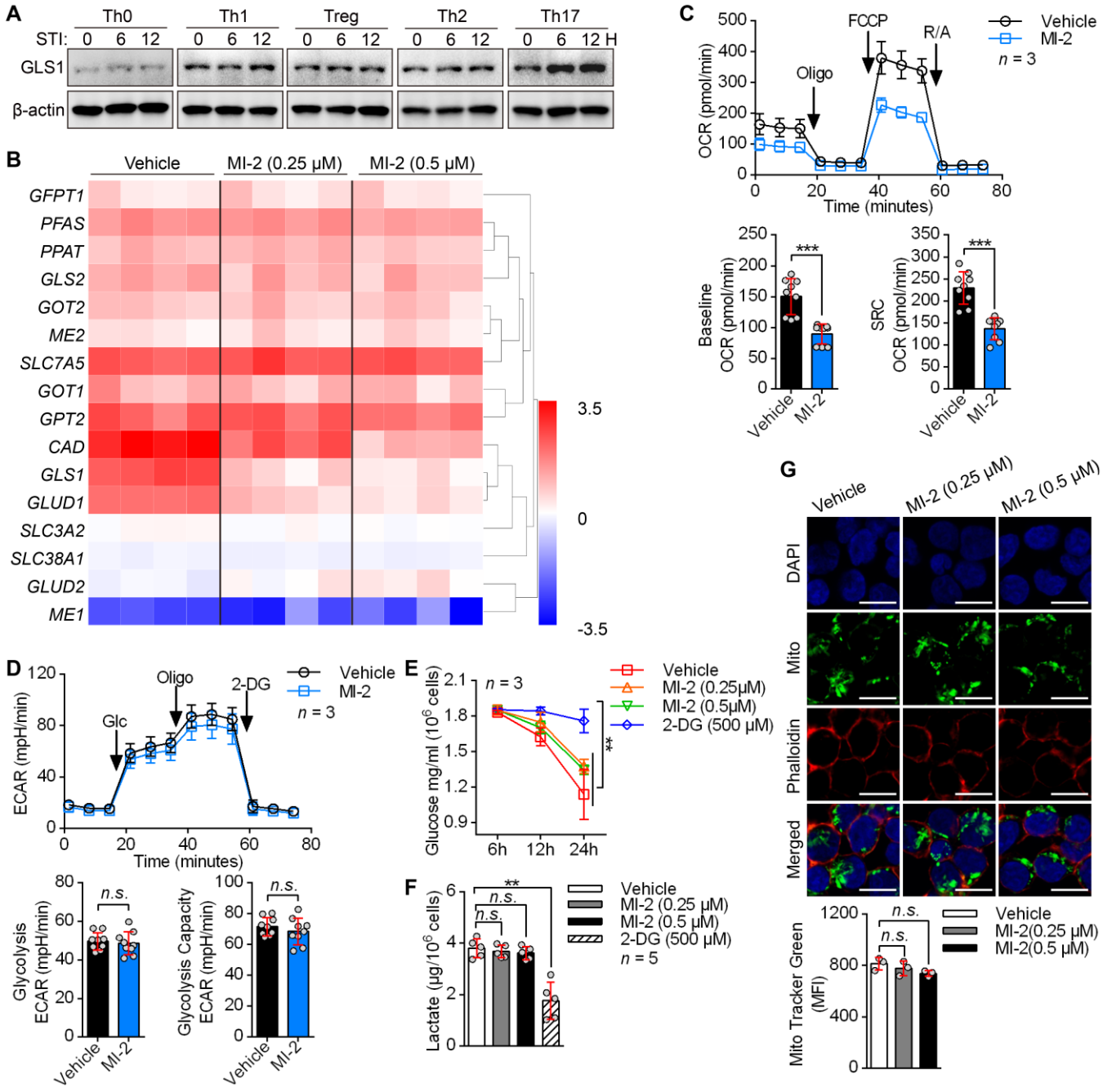
Supplemental Figure 13. Changes of metabolites when inhibiting GLS1-mediated glutaminolysis in Th17-polarizing cell. Human naïve $CD4^+$ T cells were polarized into Th17 cells for 5 days under indicated treatments. (**A**) Absolute concentrations of glutamate (n = 3). (**B**) Relative concentrations of each indicated metabolite were determined by LC-MS analysis. Cumulative data are shown (n = 3). (**C**) Absolute concentrations of acetyl-CoA in **Figure 6E** (n = 3). (**D** and **E**) Absolute concentrations of acetyl-CoA in $CD4^+$ T cells from mice in **Figure 3** (**D**, n = 5) and **Supplemental Figure 8** (**E**, n = 5). (**F** and **G**) Absolute concentrations of pyruvate (**F**) and lactate (**G**) (n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t test (**A**, **B**, **E-G**) or one-way ANOVA with Tukey's multiple comparisons test (**C** and **D**) was used to determine statistical significance (*P < 0.05, **P < 0.01, *n.s.*, not significant).



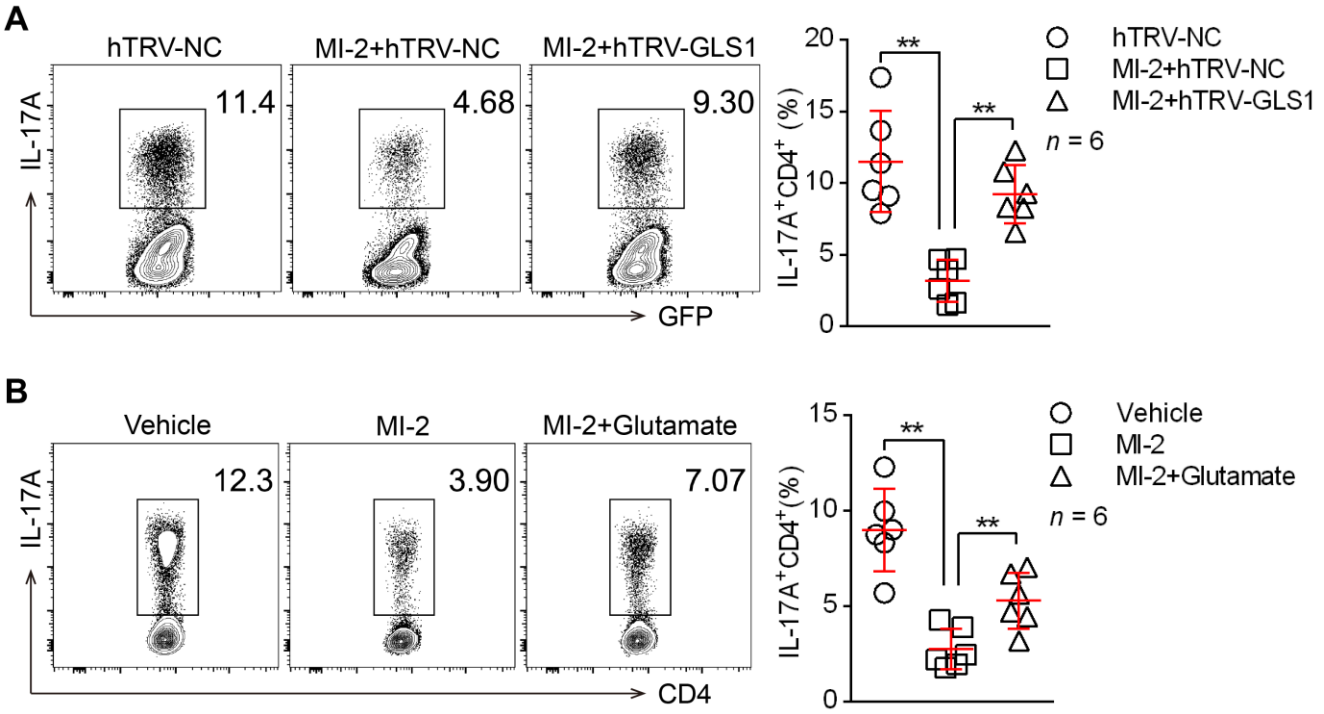
Supplemental Figure 14. GLS1-mediated glutaminolysis enhances γδ T17 differentiation via histone acetylation. Vehicle- or BPTES-treated naïve γδ T cells were polarized into γδ T17 cells for 5 days and either left untreated or supplemented with 20 mM sodium acetate for another 5 days. Acetyl-CoA concentration (**A**), the mRNA (**B**) and protein (**C**) expression of IL-17A or IL-17F (n = 3). (**D**) Histone acetylation of *Il17a* promoter regions. Results were calculated as relative to total chromatin input and normalized to total histone H3 levels to account for the nucleosomal occupancy at *Il17a* promoter regions. (**E**) RORC and AP-1 occupancy at *Il17a* gene loci (n = 3). (**F**) Representative blots for changes of RORC protein expression. Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test (**A-E**) was used to determine statistical significance (**P* < 0.05, ***P* < 0.01, ****P* < 0.001).



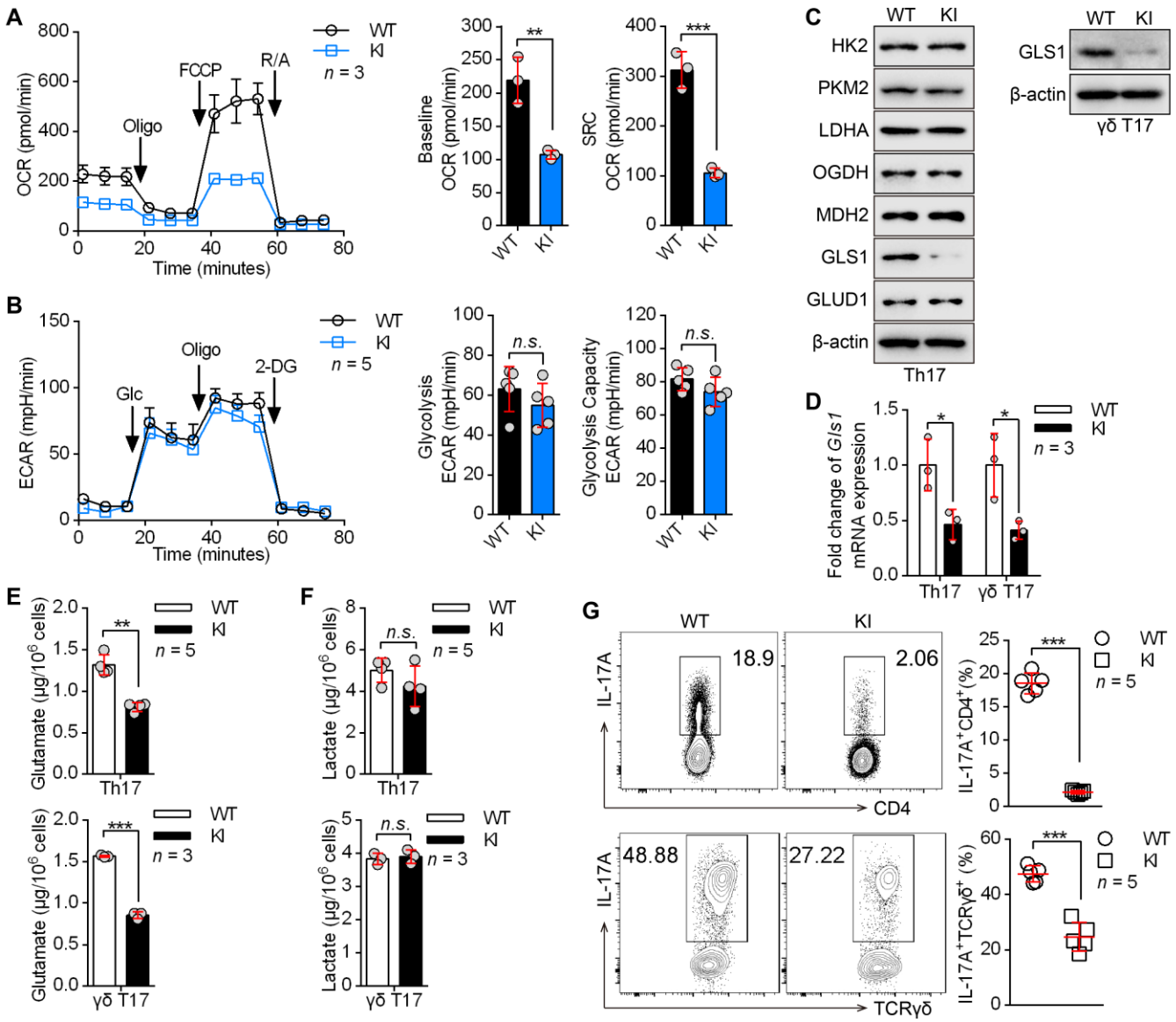
Supplemental Figure 15. MALT1 protease activity in patients with psoriasis. Western blot for the expression level and protease activity of MALT1 (cleavage of CYLD to CYLD-Ct, Bcl-10) in peripheral $CD4^+$ T cells that were collected from healthy donors and patients with psoriasis. Samples from 21 individuals of total 24 were shown. Each line represents an independent biological sample. Data are presented as mean ± SD. (*n.s.*, not significant).



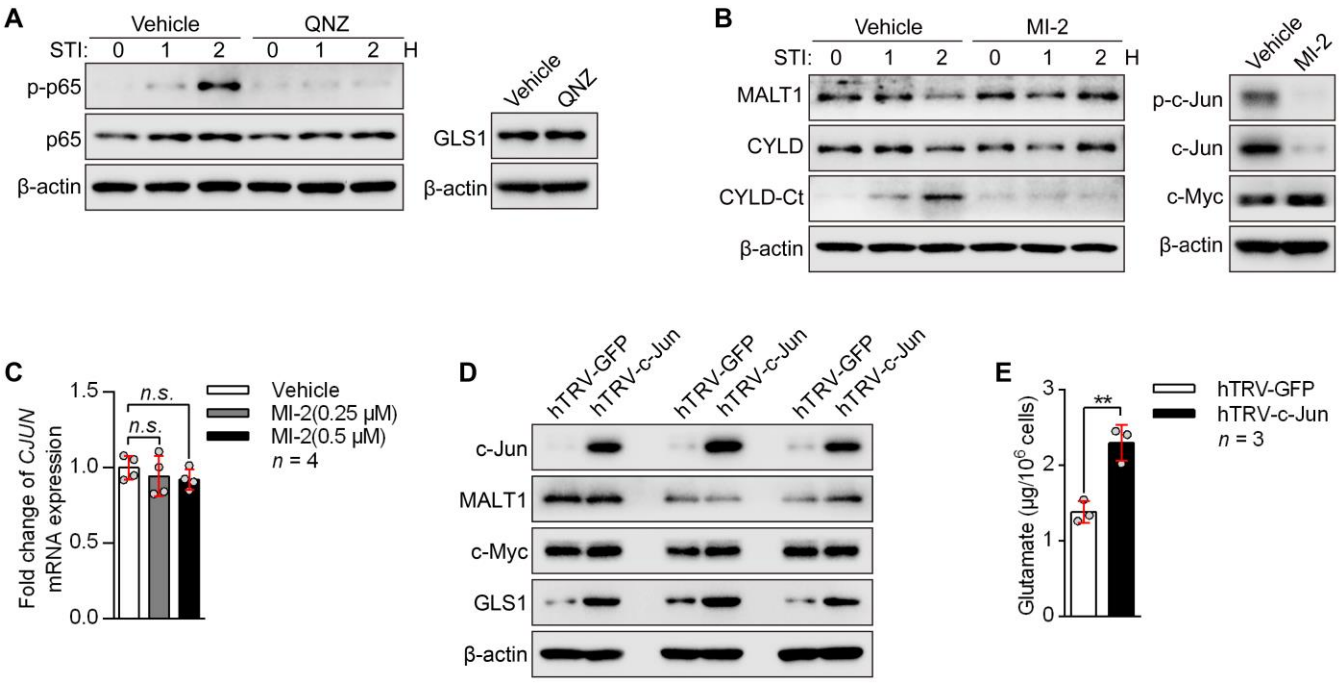
Supplemental Figure 16. Effects of MALT1 protease on cell metabolism in human Th17-polarizing cells. (**A**) Western blot for GLS1 in human Th0, Th1, Treg, Th2 and Th17 cells stimulating with CD3/CD28 for indicated times. (**B-G)** Human naïve CD4$^+$ T cells with indicated treatments were polarized into Th17 cells for 5 days. q-PCR for the mRNA expression of glutaminolysis related genes (**B**, n = 4). Seahorse analysis for mitochondrial respiration profiles, including baseline OCR and mitochondrial spare respiratory capacity (SRC) (**C**, n = 3). Seahorse analysis for Glycolysis profiles, including glycolysis and glycolysis reserve (**D**, n = 3). The consumption of glucose at indicated times (**E**, n = 3). Lactate concentration was detected (**F**, n = 5). Confocal microscopy of Th17-polarizing cells stained with MitoTracker Green (green), phalloidin (red) and the DNA-binding dye DAPI (blue). Scale bars, 10 μm. Relative intensity of MitoTracker Gren was calculated (lower panel) (**G,** n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t-test (**C** and **D**) or one-way ANOVA with Tukey's multiple comparisons test (**E-G**) was used to determine statistical significance. (**P < 0.01, ***P < 0.001, *n.s.*, not significant).



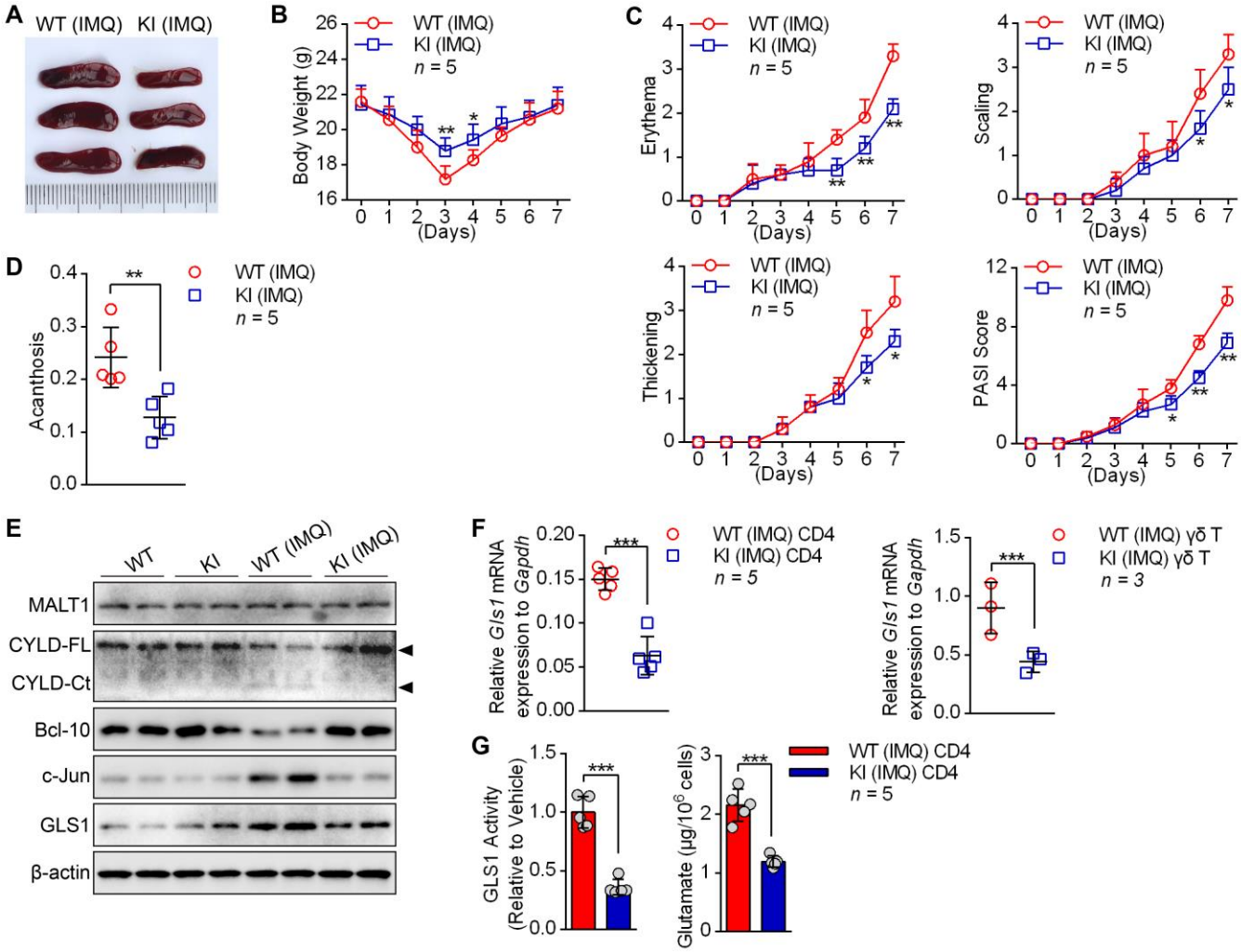
Supplemental Figure 17. MALT1 protease mediated Th17 differentiation partially relies on glutaminolysis. Vehicle- or MI-2-treated human naïve $CD4^+$ T cells were polarized into Th17 cells for 3 days, then these cells were transfected with hTRV-NC or hTRV-GLS1 (**A**, n = 6), or either left untreated or supplemented with glutamate (**B**, n = 6) for another 3 days. Flow cytometry for the percentage of Th17 cells. Statistical analysis data are shown in the right panel. Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test (**A** and **B**) was used to determine statistical significance. (**$P < 0.01$).



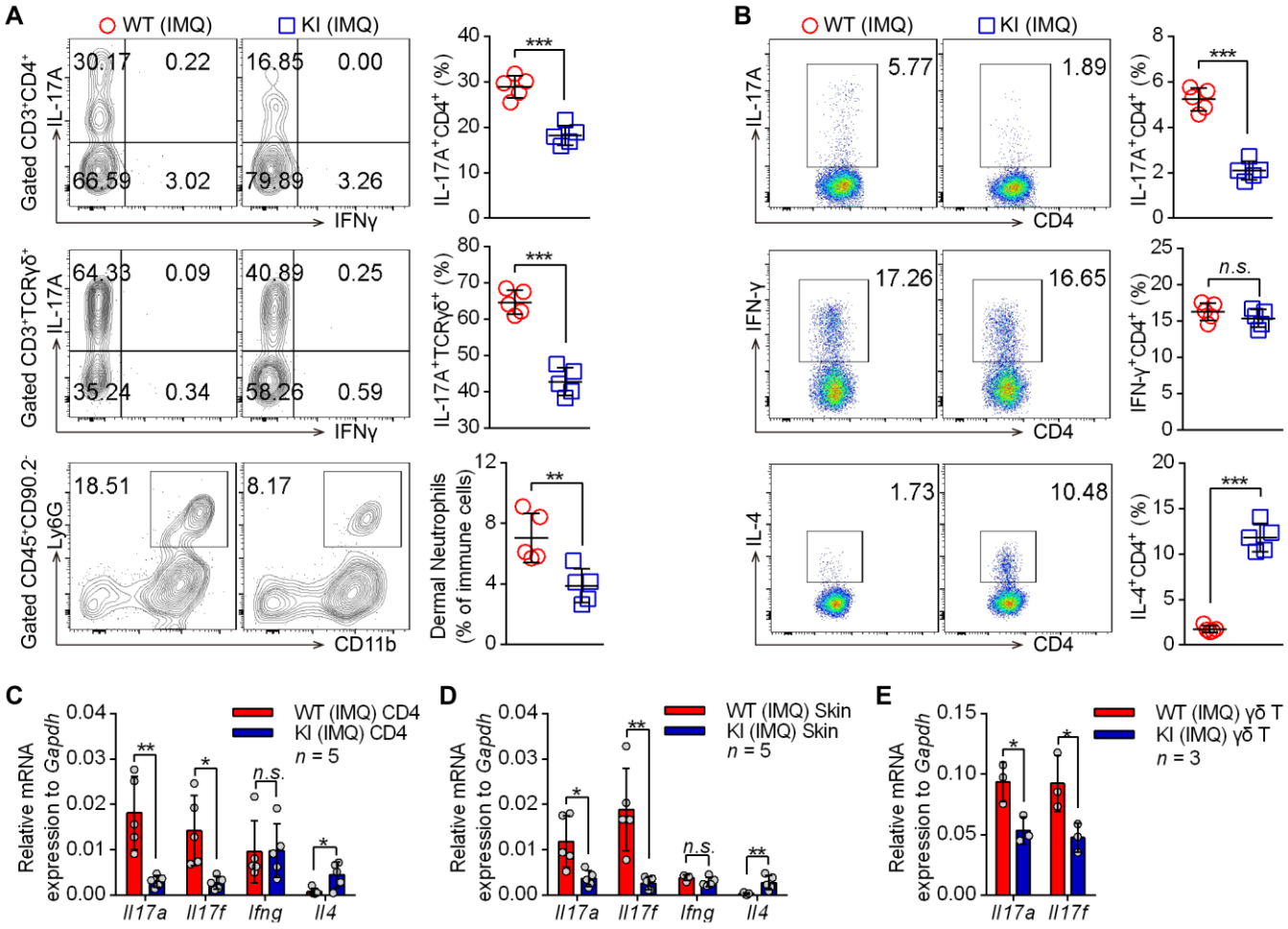
Supplemental Figure 18. Effects of MALT1 protease on cell metabolism in mouse Th17-polarizing cells. (**A and B**) Naïve CD4$^+$ T cells from WT or MALT1 protease deficiency (KI) mice were polarized into Th17 cells. Seahorse analysis for mitochondrial respiration profiles, including baseline OCR and mitochondrial spare respiratory capacity (SRC) (**A**, n = 3). Seahorse analysis for glycolysis profiles, including glycolysis and glycolysis reserve capacity (**B**, n = 5). (**C-G**) Naïve CD4$^+$ or γδ T cells from WT or MALT1 protease deficiency (KI) mice were polarized into Th17 cells or γδ T17 cells. The protein (**C**) and mRNA (**D**) levels of key metabolic enzymes were detected. Glutamate (**E**) and lactate concentration (**F**) was detected by assay kits (n = 5 or 3). (**G**) Flow cytometry for the percentage of Th17 and γδ T17 cells. Statistical analysis data are shown in the right panel (n = 5). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. Two-tailed unpaired Student's t-test was used to determine statistical significance. (**P < 0.01, ***P < 0.001, *n.s.*, not significant).



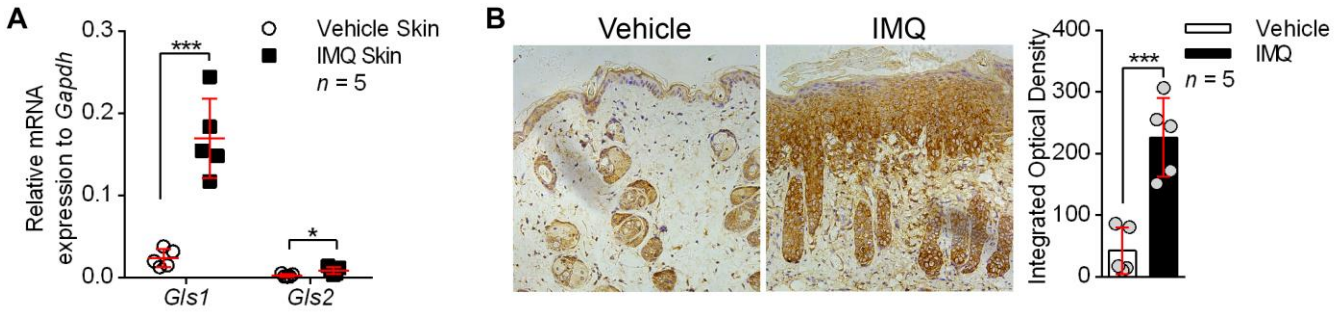
Supplemental Figure 19. Regulation of MALT1 protease activity, c-Jun and GLS1. (**A**-**C**) Human naïve $CD4^+$ T cells were treated with indicated inhibitors or not and polarized into Th17 cells for 5 days. Western blot for NF-κB activity in response to anti-CD3/CD28 stimulation (left panel) and GLS1 expression (right panel) (**A**). Western blot for MALT1 protease activity in response to anti-CD3/CD28 stimulation (left panel) and expression of p-c-Jun, c-Jun and c-Myc (right panel) (**B**). q-PCR for the mRNA expression of *CJUN* (**C**, n = 4). (**D** and **E**) Human naïve $CD4^+$ T cells were transfected with hTRV-NC or hTRV-GLS1 and polarized into Th17 cells for 5 days. Western blot for expression of c-Jun, MALT1, c-Myc and GLS1 (**D**). Glutamate concentration was determined by assay kit (**E**, n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test (**C**) or two-tailed unpaired Student's t-test (**E**) was used to determine statistical significance. (**$P < 0.01$, *n.s.*, not significant).



Supplemental Figure 20. MALT1 protease deficiency (KI) mice showed ameliorated pathogenesis in IMQ-induced psoriasis. WT or MALT1 protease deficiency (KI) mice were painted on the shaved back skin with IMQ cream for 7 consecutive days. Splenomegaly (**A**), body weight(**B**), PASI score (**C**) and acanthosis (**D**) were presented (n = 5). Western blot for MALT1 protease activity, GLS1 and c-Jun expression in dermal γδ T cells (**E**). q-PCR for *Gls1* mRNA expression in splenic $CD4^+$ T cells and dermal γδ T cells (**F**, n = 5 or 3). GLS1 activity and glutamate concentration in splenic $CD4^+$ T cells (**G**, n = 5). Data are presented as mean ± SD and represent one of three independent experiments with consistent results. Two-tailed unpaired Student's t-test was used to determine statistical significance. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

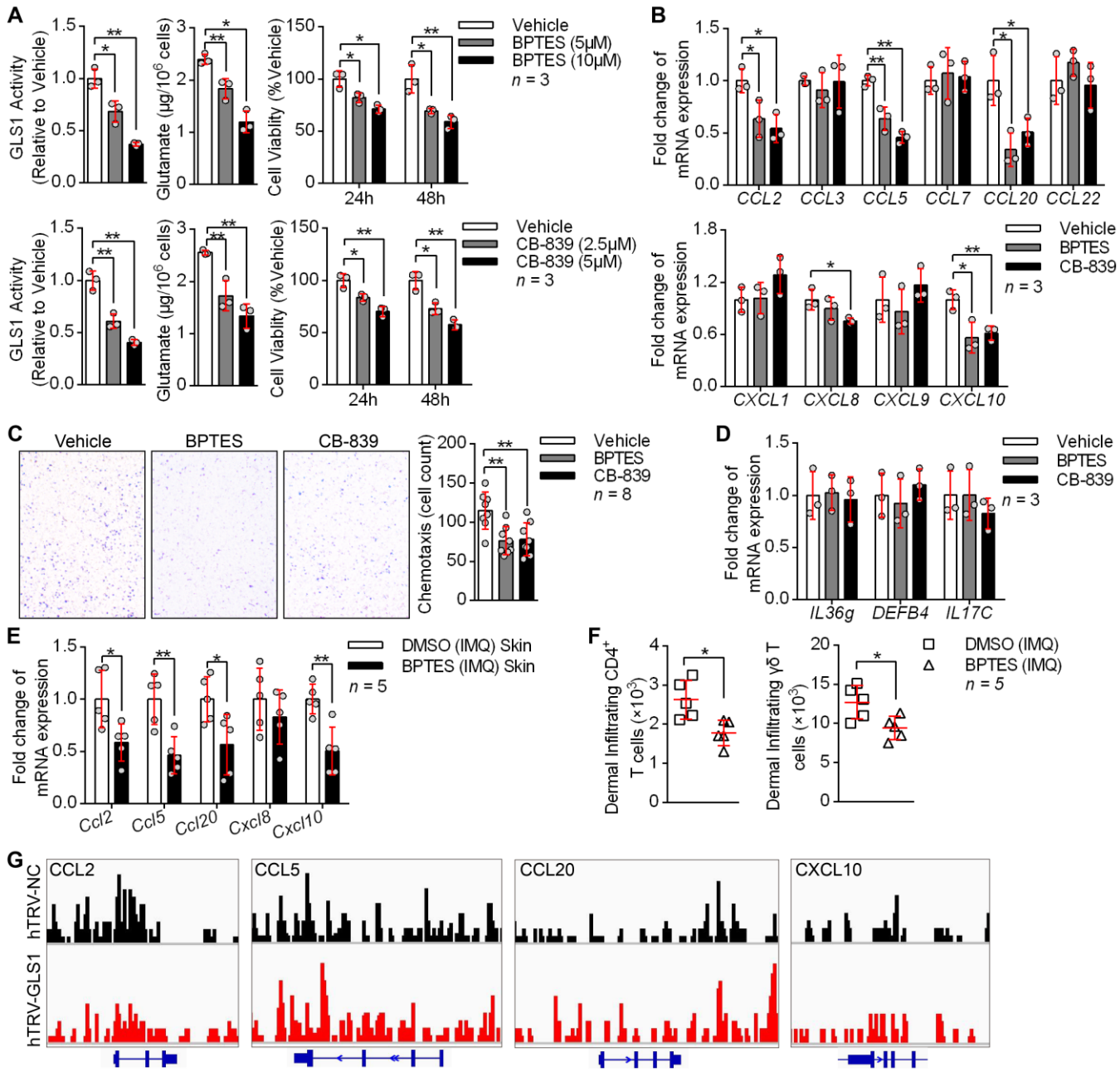


Supplemental Figure 21. MALT1 protease deficiency (KI) mice showed decreased inflammation in IMQ-induced psoriasis. (**A**) Flow cytometry for the percentage of IL-17A$^+$ in dermal CD4 and γδ T cells, neutrophils in dermal CD45$^+$ lymphocytes in **Supplementary Figure 20**. Statistical data are shown in the lower panel (n = 5) (**B**) Flow cytometry for the percentage of Th17, Th1 and Th2 in splenic CD4 T cells in **Supplementary Figure 20**. Statistical data are shown in the lower panel (n = 5). (**C**) The relative mRNA expression of *Il17a, Il17f, Ifng* and *Il4* in splenic CD4$^+$ T cells (n = 5), skin (n = 5) or dermal γδ T cells (n = 3) in **Supplementary Figure 20**. Data are presented as mean ± SD and represent one of three independent experiments with consistent results. Two-tailed unpaired Student's t-test was used to determine statistical significance. (*P < 0.05, **P < 0.01, ***P < 0.001, *n.s.*, not significant).

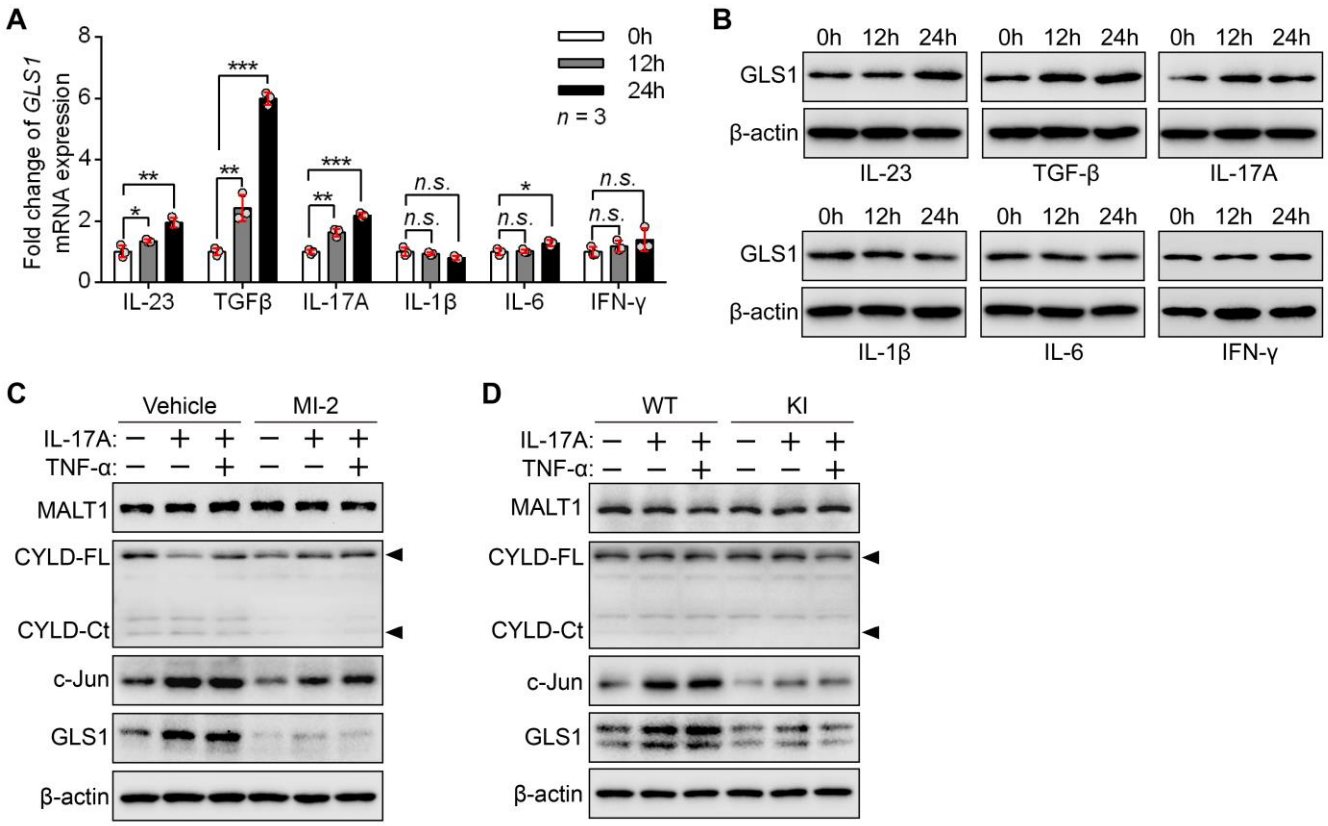


Supplemental Figure 22. GLS1 expression in normal and IMQ-treated mouse skin.

(**A**) qPCR for mRNA expression of GLS1 and GLS2 in skin derived from vehicle- and IMQ-treated mice (n = 5). (**B**) IHC for expression of GLS1 in skin derived from vehicle- and IMQ-treated mice. Integrated optical density was calculated and statistical data are shown in the right panel (n = 5). Data are presented as mean ± SD and represent one of three independent experiments with consistent results. Two-tailed unpaired Student's t-test was used to determine statistical significance. (*$P < 0.05$, ***$P < 0.001$).



Supplemental Figure 23. Inhibition of GLS1-mediated glutaminolysis restrains proliferation and chemotaxis of keratinocytes. (**A-D**) HaCaT cells were either left untreated or treated with BPTES or CB-839 for indicated time. GLS1 activity, glutamate concentration and proliferation of HaCaT cells were presented (**A**, n = 3). q-PCR for mRNA expression of chemokines in HaCaT cells (**B**, n = 3). The culture supernatants were collected at 48 h and added to the lower chambers, and normal human $CD4^+$ T cells were added to the upper chambers of trans-well plates for 2 h. The upper chamber was removed and stained with crystal violet, and cells were counted (**C**, n = 5). q-PCR for mRNA expression of *IL36G*, *DEFB4* and *IL17C* in HaCaT cells (**D**, n = 3). (**E** and **F**) The mRNA levels of chemokines in epidermis (**E**) and quantification of dermal infiltrating $CD4^+$ and γδ T cells (**F**) from mice in **Figure 3** (n = 5). (**G**) Chip-seq for histone acetylation (H3K9Ac) of indicated gene in HaCaT cells with GLS1over-expression or not (n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's multiple comparisons test (**A-D**) or two-tailed unpaired Student's t-test (**E** and **F**) was used to determine statistical significance. (*$P < 0.05$, **$P < 0.01$).



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645 **Supplemental Figure 24. MALT1 protease activity is essential for IL-17A-induced GLS1 expression in**
646 **keratinocytes.** (**A** and **B**) HaCaT cells were stimulated with IL-23 (20 ng/ml), TGF-β (5 ng/ml), IL-17A (200
647 ng/ml), IL-1β (10 ng/ml), IL-6 (10 ng/ml) and IFN-γ (200 ng/ml) for 0 h, 12 h and 24 h. q-PCR for mRNA
648 expression of GLS1 (**A**, n = 3). Western blot for protein level of GLS1 (**B**). (**C** and **D**) MI-2 treated HaCaT cells (**C**)
649 and primary keratinocytes from WT or KI mice (**D**) were stimulated with IL-17A or plus TNF-α for 24 hours.
650 Representative blots for MALT1 protease activity, GLS1 and c-Jun expression. Data are presented as mean ± SD
651 and represent one of at least two independent experiments with consistent results. One-way ANOVA with Tukey's
652 multiple comparisons test (**A**) was used to determine statistical significance. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$,
653 *n.s.*, not significant).
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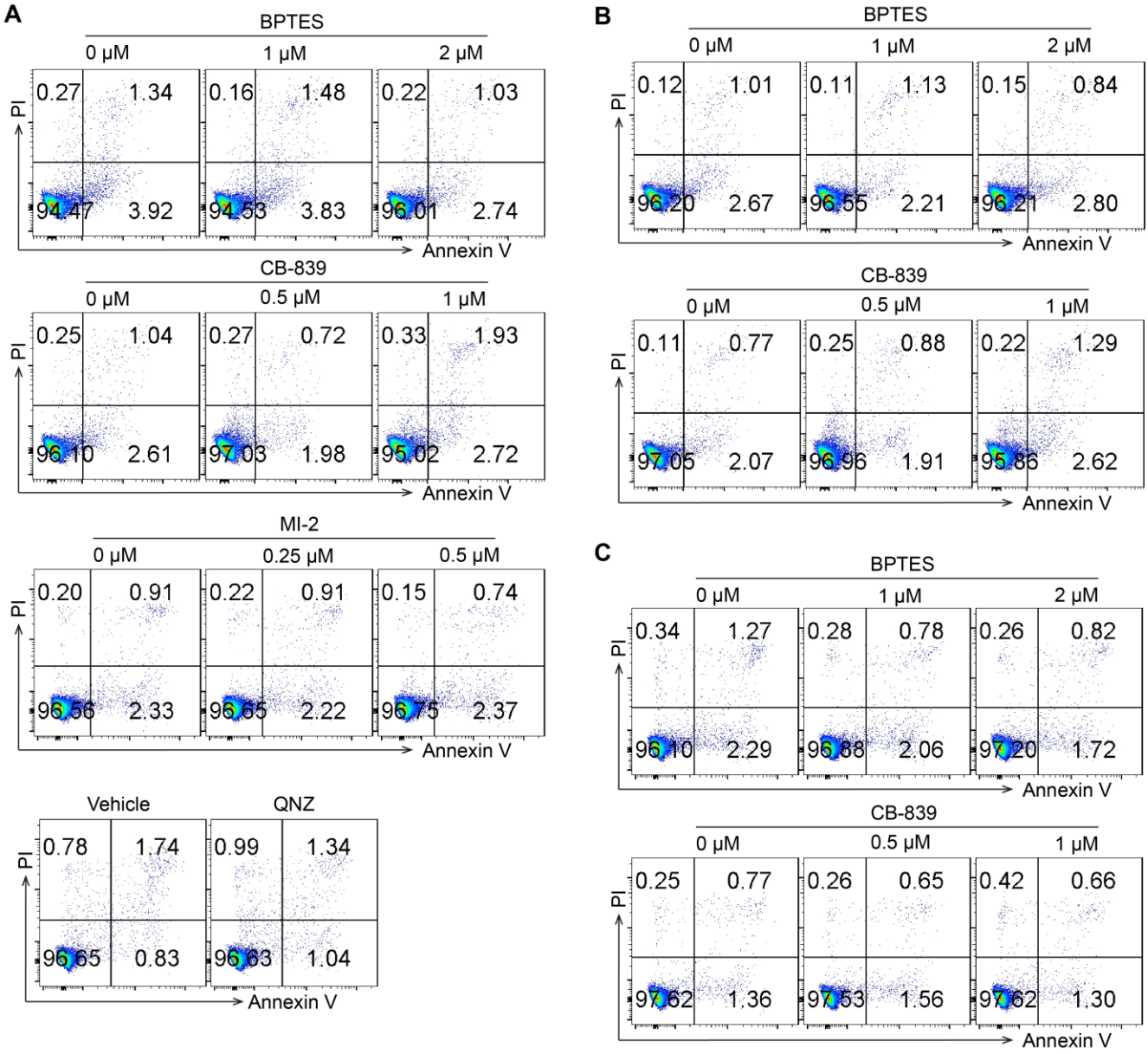

Supplemental Figure 25. The viability measures of cells treated with chemical inhibitors in vitro. (**A)** Human naïve $CD4^+$ T cells were treated with BPTES, CB-839, MI-2 or QNZ at indicated concentration and polarized into Th17 cells for 5 days. The cell viability was measured by FACS using PI/Annexin V kit (n = 3). (**B**) Mouse naïve $CD4^+$ T cells were treated with BPTES or CB-839 at indicated concentration and polarized into Th17 for 5 days. The cell viability was measured by FACS using PI/Annexin V kit (n = 3). (**C**) Mouse naïve γδ T cells were treated with BPTES or CB-839 at indicated concentration and polarized into γδ T17 for 5 days. The cell viability was measured by FACS using PI/Annexin V kit (n = 3). Data are presented as mean ± SD and represent one of at least two independent experiments with consistent results.

673 **Supplementary Table 1. Information for patients with psoriasis vulgaris.**

674

Sample ID	Gender	Age	PASI score
1	M	49	6.7
2	F	56	21.7
3	M	20	15.4
4	M	64	3.5
5	F	59	11.9
6	M	48	12.4
7	M	56	10.6
8	F	21	9.6
9	M	43	9.5
10	M	73	13.4
11	M	47	12.4
12	M	45	13.8
13	F	52	1.6
14	M	30	7.5
15	F	63	3.3
16	F	40	4.9
17	M	36	10.6
18	M	44	5.5
19	F	21	9.6
20	F	30	1.2
21	F	48	20.8
22	M	55	10.2
23	F	28	5.4
24	F	50	5.6
25	F	38	7.9
26	M	42	11.3
27	M	59	13.8
28	F	41	15.7
29	M	57	10.4
30	F	63	17.6
31	F	53	10.6
32	M	37	6.2
33	F	41	4.9
34	M	34	3.4
35	F	47	9.3
36	M	55	12.0

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676 All patients were clinically diagnosed as psoriasis vulgaris. M, male; F, female;
677 PASI: psoriasis area and severity index.

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Supplemental Table 2. Quantitative PCR primer sequences.

Primer name	**Forward Primer** (5' to 3')	**Reverse Primer** (5' to 3')
Human *IFNG*	CATCCAAAAGAGTGTGGAGACA	TGCTTTGCGTTGGACATTCAAG
Human *IL4*	GGTCACAGGAGAAGGGACGCC	TGCGAAGCACCTTGGAAGCCC
Human *IL17A*	AGATTACTACAACCGATCCACCT	GGGGACAGAGTTCATGTGGTA
Human *IL17F*	GCGTTTCCATGTCACGTAACA	CAGCCCAAGTTCCTACACTGG
Human *TBX21*	CAGGGACGGCGGATGTTCC	TCCACACTGCACCCACTTGC
Human *RORC*	CTGGGCATGTCCCGAGATG	GAGGGGTCTTGACCACTGG
Human *FOXP3*	CTTTCACCTACGCCACGCTCAT	TCCAGGTGGCAGGATGGTTTCT
Human *GLS1*	AGGGTCTGTTACCTAGCTTGG	ACGTTCGCAATCCTGTAGATTT
Human *GLS2*	GGCCATGTGGATCGCATCTT	ACAGGTCTGGGTTTGACTTGG
Human *CJUN*	TCCAAGTGCCGAAAAAGGAAG	CGAGTTCTGAGCTTTCAAGGT
Human *IL36G*	AGGAAGGGCCGTCTATCAATC	CACTGTCACTTCGTGGAACTG
Human *DEFB4*	AGACTTGTGCTGCTATTAGCCG	GGGCAGTCCCATAACCACATA
Human *IL17C*	CCACACTGCTACTCGGCTG	CACACGGTATCTCCAGGGTGA
Human *GAPDH*	ATGGGGAAGGTGAAGGTCG	GGGGTCATTGATGGCAACAATA
Mouse *Ifng*	AGACAATCAGGCCATCAGCA	CAACAGCTGGTGGACCACTC
Mouse *Il4*	GGTCTCAACCCCCAGCTAGT	GCCGATGATCTCTCTCAAGTGAT
Mouse *Il17a*	ATGCTGTTGCTGCTGCTGAG	GGAAGTCCTTGGCCTCAGTG
Mouse *Il17f*	GGAGGTAGCAGCTCGGAAGA	GGAGCGGTTCTGGAATTCAC
Mouse *Tbx21*	CAACAACCCCTTTGCCAAAG	TCCCCCAAGCAGTTGACAGT
Mouse *Rorc*	GGACAGGGAGCCAAGTTCTCA	CACAGGTGATAACCCCGTAGTGG
Mouse *Foxp3*	TTGCCAAGCTGGAAGACTGC	CAGACGGTGCCACCATGACT
Mouse *Gls1*	GTCCTGAGGCAGTTCGGAATACAC	GAGGAGGAGACCAACACATCATGC
Mouse *Gls2*	CATGCTGCCTCGACTTGGTGAC	GAGCCGTGGTGAACTTGTGGATAG
Mouse *Gapdh*	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA

Supplemental Table 3. ChIP-qPCR primers.

For H3K9Ac, H3K27Ac and H3		
Primer name	Forward Primer (5' to 3')	Reverse Primer (5' to 3')
Human *IL17A*	GTGTCACCCCTGAACCCACT	GGATGGATGAGTTTGTGCCTGC
Mouse *Il17a*	CAGGTATTATTCTCAGGGCTTTGG	TGGCAATGGTGTCTTTTCTTTG
For RORC		
Primer name	Forward Primer (5' to 3')	Reverse Primer (5' to 3')
Human *IL17A*	GCAGCTCTGCTCAGCTTCTA	GGGCTTTTCTCCTTCTGTGG
Mouse *Il17a*	GCATAGTGAACTTCTGCCCT	GTAGTGCTCCTTTCTCTCTTT
For AP-1		
Primer name	Forward Primer (5' to 3')	Reverse Primer (5' to 3')
Mouse *Il17a*	CATGTTTGACTGTGCACGAG	TCTTACATTCTTTTTGTGAC
For c-Jun		
Primer name	Forward Primer (5' to 3')	Reverse Primer (5' to 3')
Human *GLS1*-p1	AGGGTCTGTTACCTAGCTTGG	ACGTTCGCAATCCTGTAGATTT
Human *GLS1*-p2	GCGTGCAGAAAGTGGCTACTGAGC	CTCTCGGCTCTGGGTGCGCGGAGAG
Human *GLS1*-p3	CCTCGGAGTTGGCACGGCGTGCAG	GGCAGTCAAATTTCTCTCGGCTC