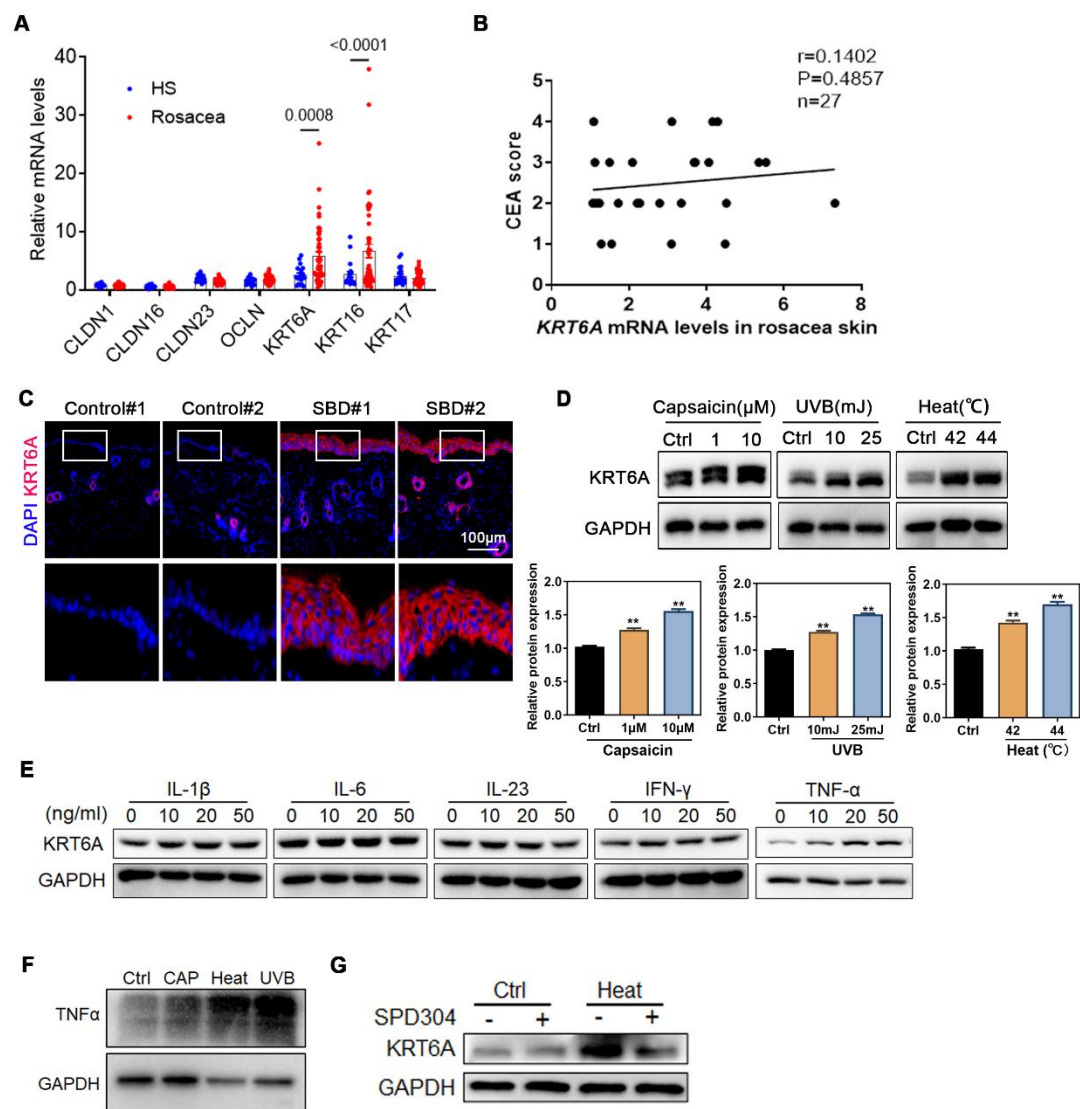


1 **SUPPLEMENTARY MATERIALS**



2

3 Figure S1. KRT6A is up-regulated in irritated conditions of rosacea and

4 psoriasis.

5 (A) The mRNA levels of skin barrier alarms in rosacea lesions(n=16) and

6 healthy controls(n=19). (B) Correlation analysis between KRT6A expression

7 and CEA score in rosacea lesions. (C) Representative IF images showing the

8 expression of KRT6A in the skin of mice with skin barrier dysfunction by

9 tape-stripping. SBD: skin barrier dysfunction. (D) Representative western

blot images showing the expression of KRT6A in HaCaT cells treated with
 capsaicin, UVB, or high temperatures. Quantification of relative protein
 expression is shown in the bottom panel. (E) Representative western blot
 images showing the expression of KRT6A in HaCaT cells treated with various
 concentration of IL-1 β , IL-6, IL-23, IFN- γ or TNF- α . (F) Representative western
 blot images showing the expression of TNF α in HaCaT cells treated with
 capsaicin, UVB, or high temperatures. (G) Representative western blot images
 showing the expression of KRT6A in HaCaT cells treated with high
 temperatures and with or without SPD304 (2 μ M). Two-tailed unpaired
 Student's t-test (D) was used. All experiments were performed in 3
 independent biological replicates. Data represents the mean \pm SD. * p < 0.05,
 ** p < 0.01. Two-tailed unpaired Student's t-test (D) was used.

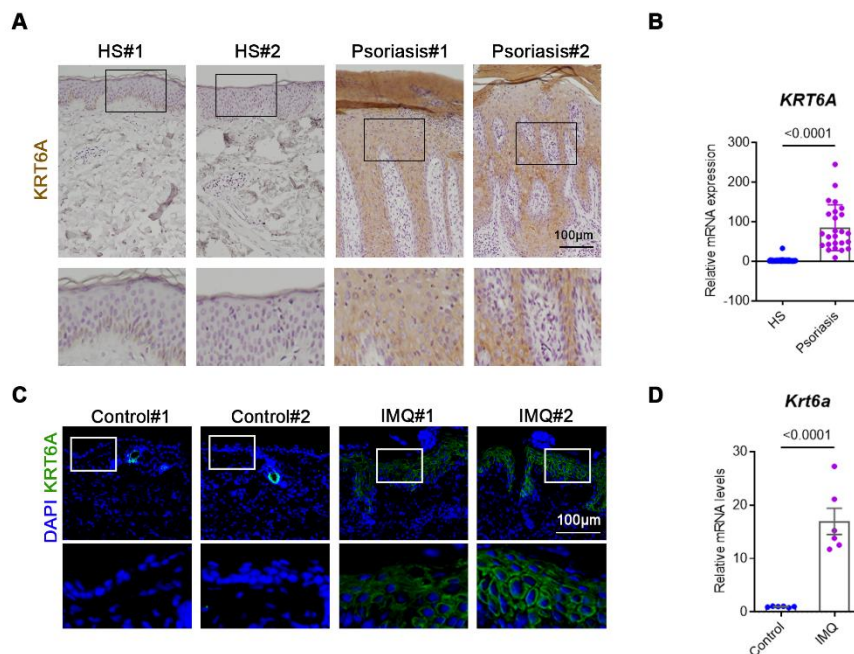
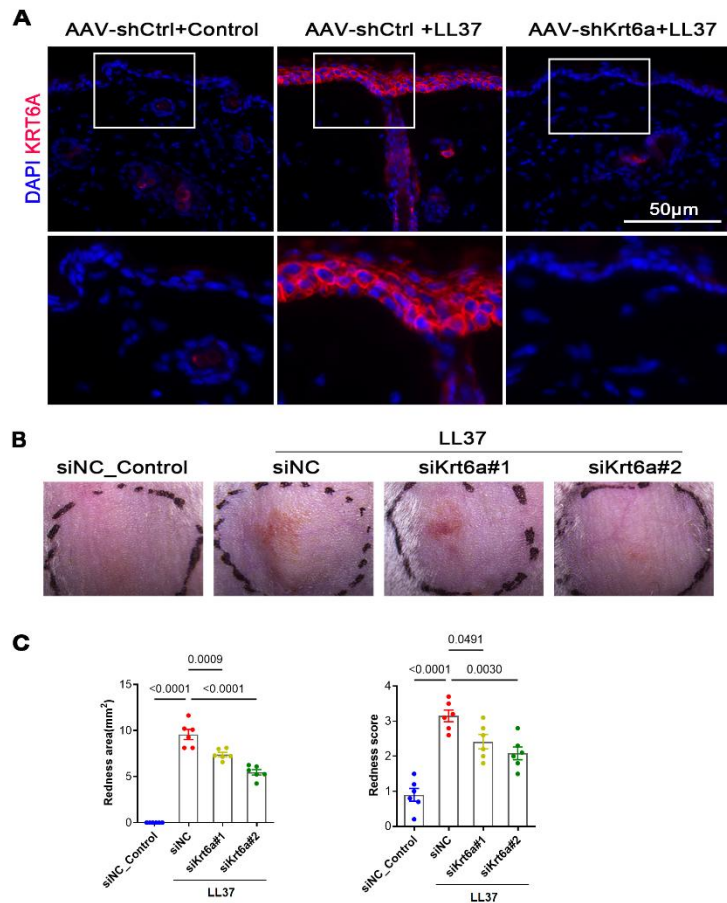


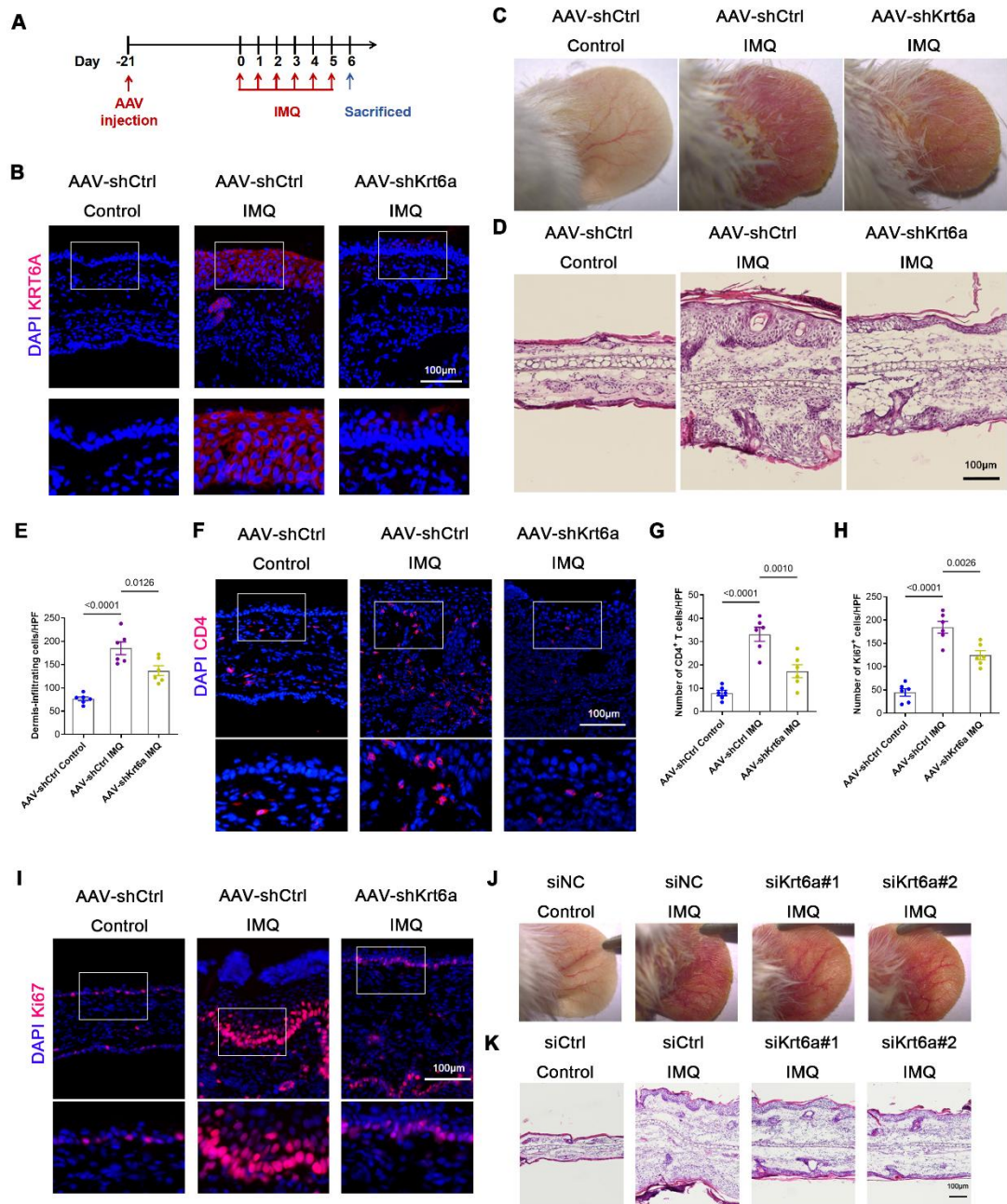
Figure S2. KRT6A is up-regulated in psoriasis.
 (A) Representative IHC images showing the expression of KRT6A in psoriasis

25 lesions and healthy controls. (B) The mRNA levels of KRT6A in psoriasis
 26 lesions and healthy controls from the GEO database (GSE121212). IF images
 27 (C) and RT-qPCR analysis (D) showing the expression of KRT6A in the skin of
 28 IMQ-induced psoriasis-like mice and controls.



29
 30 Figure S3. KRT6A knockdown relieves the development of rosacea.
 31 (A) The knockdown efficiency of KRT6A by AAV in LL37-treated mice. (B) The
 32 back skins of the control group and siRNA-mediated knockdown of the Krt6a
 33 group treated with or without LL37 (n=6/group). Images were taken 48 hr after
 34 the first LL37 injection. (C)The redness score and redness area of the back
 35 skin of mice in (B). Data represents the mean \pm SEM. The one-way ANOVA

36 with Bonferroni's post hoc tests was used for multiple comparisons.



37

38 Figure S4. KRT6A knockdown relieves the development of psoriasis.

39 (A) Schematic diagram of AAV-shKrt6a-injected mice treated with IMQ or
 40 control. (B) The knockdown efficiency of Krt6a by AAV in IMQ-treated mice. (C)
 41 Ear skin of mice in control group and Krt6a-knockdown group treated with IMQ
 42 (n=6/group). (D) HE staining and (E) dermal infiltrating cell counts of the ear in

43 mice. The CD4+ T cell infiltration (F) and cell counts (G) in skin visualized by IF.

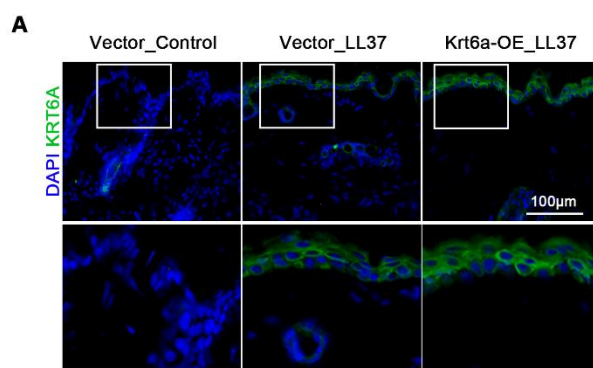
44 The Ki67+ cells (H) and cell counts (I) in the skin visualized by IF. (J) The ear

45 skins of the control group and siRNA-mediated knockdown of the Krt6a group

46 treated with or without IMQ (n=6/group). (K) HE staining of the ear in mice.

47 Data represents the mean \pm SEM. The one-way ANOVA with Bonferroni's post

48 hoc tests was used for multiple comparisons.



49

50 Figure S5. The efficiency of Krt6a overexpression by lentivirus in LL37-treated

51 mice.

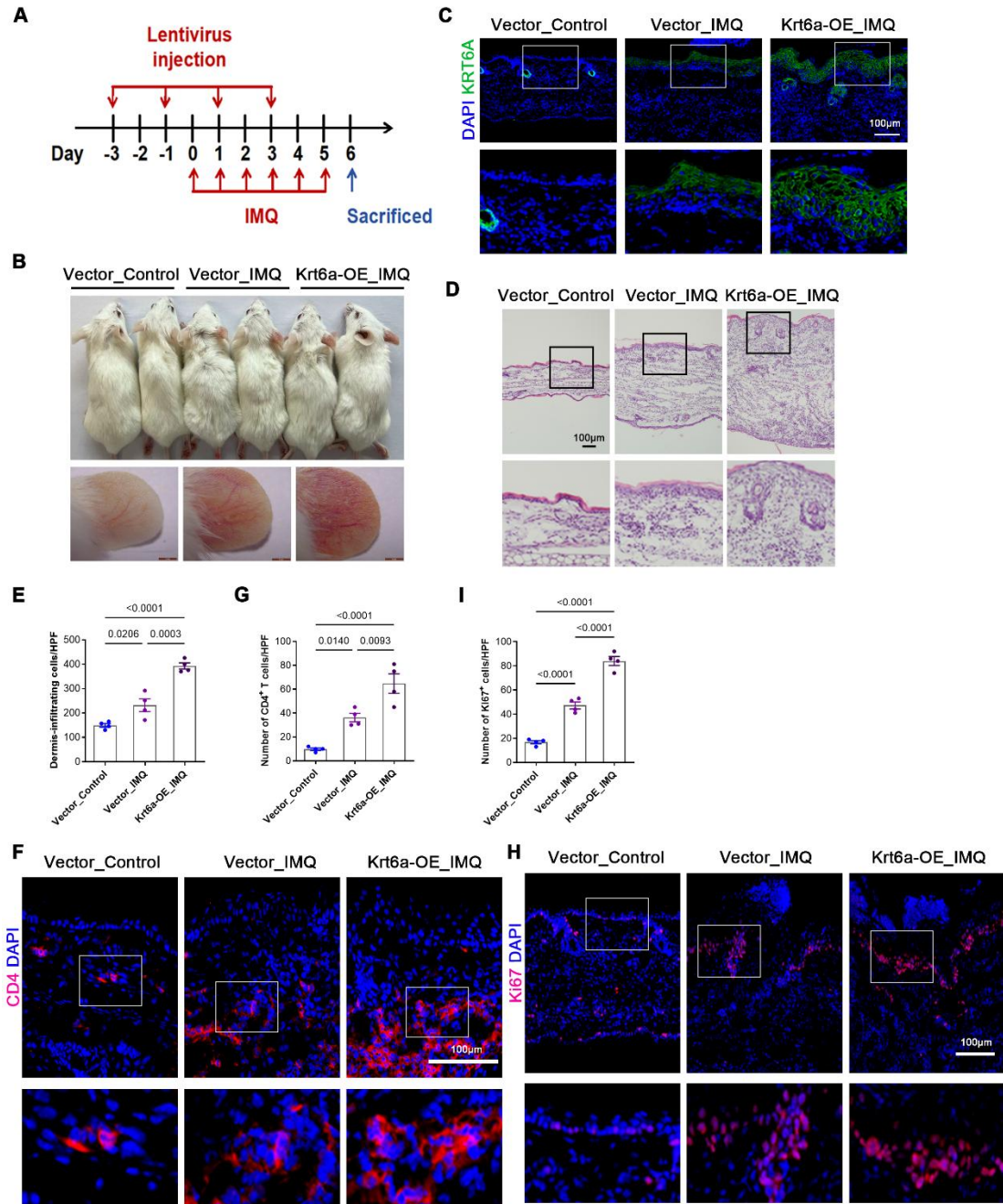


Figure S6. KRT6A promotes the development of psoriasis.

(A) Schematic diagram of lentivirus-injected mice treated with IMQ or control.

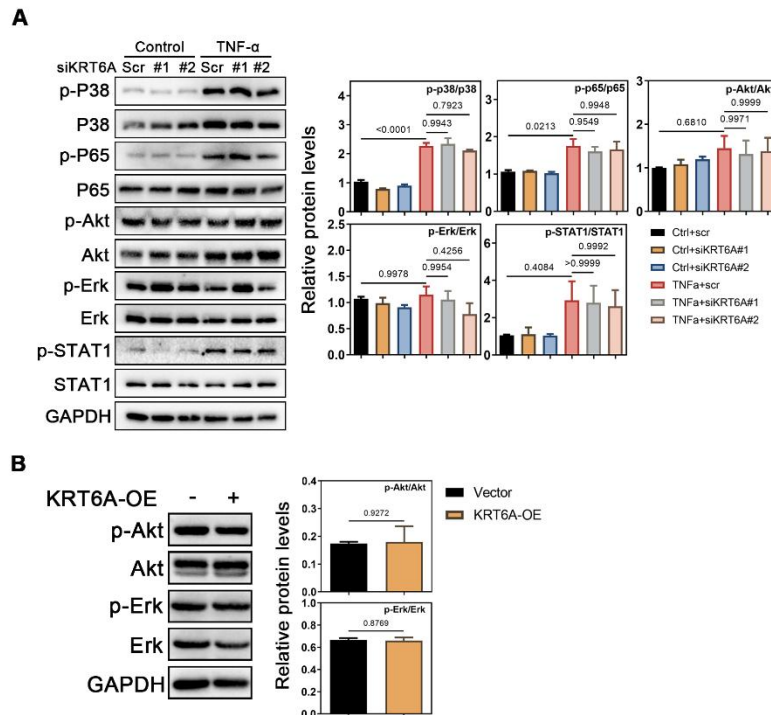
(B) Ear skin of mice in the control group and Krt6a-overexpressed group

treated with IMQ. (C) Krt6a overexpressed by lentivirus in IMQ-treated mice.

(D) HE staining and (E) dermal infiltrating cell counts of the ear in mice. (F) The

CD4+ T cell infiltration and (G) cell counts in the skin visualized by IF. (H) The

59 Ki67+ cells, and cell counts (I) in skin visualized by IF. Data represents the
60 mean \pm SEM. The one-way ANOVA with Bonferroni's posthoc tests was used
61 for multiple comparisons.



62
63 Figure S7. KRT6A affects STAT3 activation in keratinocytes.

64 (A) Immunoblotting of p-STAT1, STAT1, p-p65, P65, p-p38, P38, p-AKT, AKT,
65 p-ERK or ERK in cell lysates from HaCaT cells infected with siKRT6A or Scr
66 and stimulated with TNF- α for 2 hours. Quantification of relative protein
67 expression is shown in the right panel. (B) Immunoblotting of p-AKT, AKT,
68 p-ERK or ERK in cell lysates from KRT6A-overexpressed HaCaT cells.
69 Quantification of relative protein expression is shown in the right panel.
70 All experiments were performed in 3 independent biological replicates. Data
71 represents the mean \pm SEM. Two-tailed unpaired Student's t-test (B) or 1-way
72 ANOVA with Bonferroni's post hoc test (A) was used.

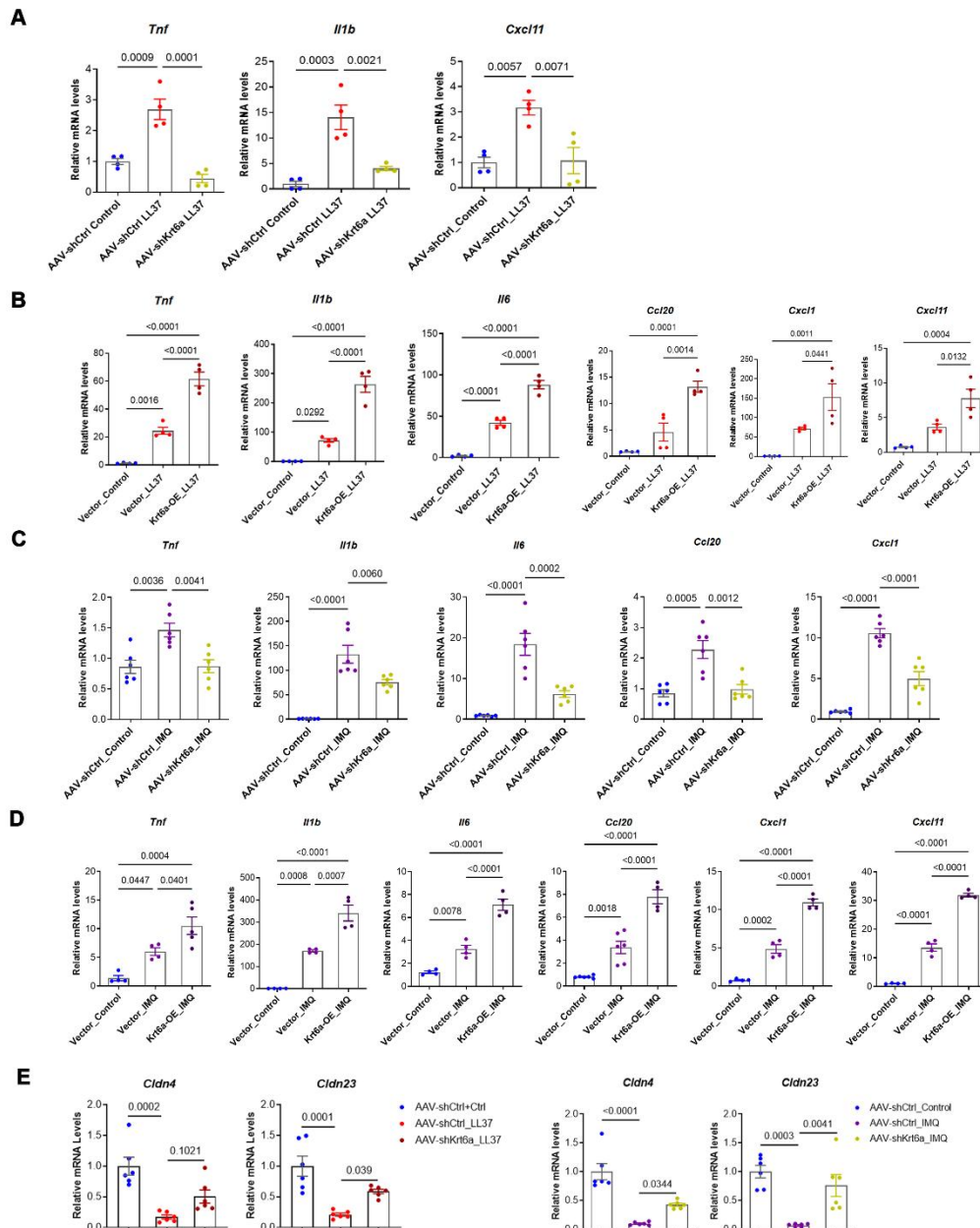
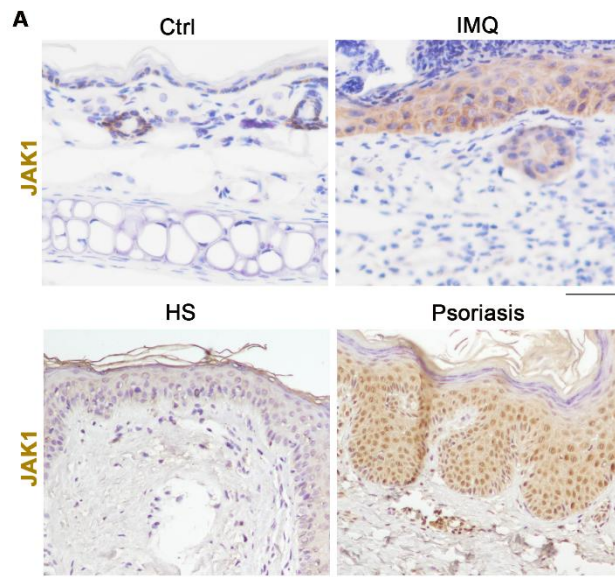


Figure S8. KRT6A affects cytokine expression in vivo.

The mRNA levels of cytokines in LL37-induced mice combined with Krt6a knockdown (A) or overexpression (B). The mRNA levels of cytokines in IMQ-induced mice combined with Krt6a knockdown (C) or overexpression (D). (E) The mRNA levels of *Cldn4* and *Cldn23* in LL37/IMQ-induced mice combined with Krt6a knockdown. Data represents the mean \pm SEM. The

80 one-way ANOVA with Bonferroni's posthoc tests was used for multiple
81 comparisons.



82
83 Figure S9. JAK1 expression in human and mouse models of psoriasis
84 Representative IHC images showing the expression of JAK1 in psoriatic
85 lesions and healthy controls in the upper panel; Representative IHC images
86 showing the expression of JAK1 in IMQ-induced rosacea-like mice in the
87 bottom panel.

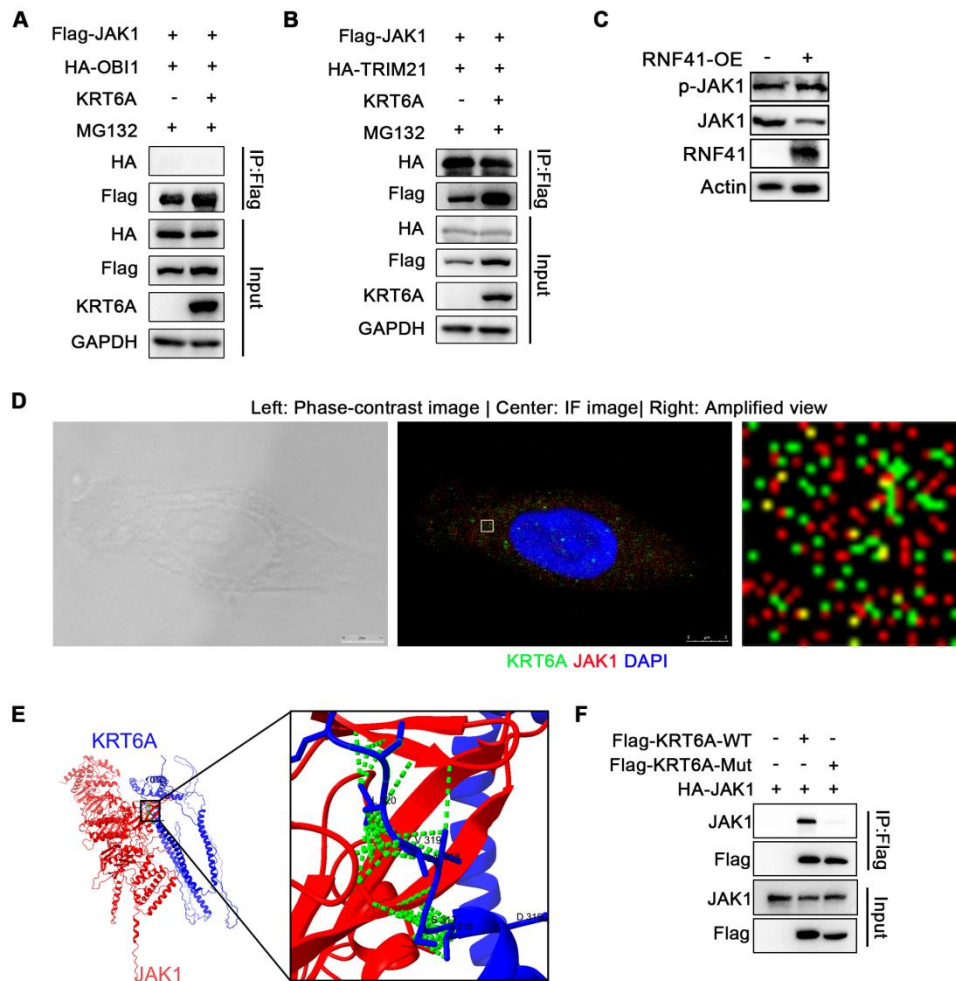


Figure S10. HA-OBI1 plasmid (A) or HA-TRIM21 plasmid (B) combined with Flag-JAK1 plasmid was transfected into HEK293T cells with or without KRT6A plasmid to detect the interaction between JAK1 and the target protein. (C) RNF41 plasmid was transfected into HaCaT cells. (D) Representative images showing the localization of KRT6A and JAK1 in HaCaT cells. Left: Corresponding phase-contrast image confirming intact cell morphology and the spatial localization of the fluorescence signals. Center: Immunofluorescence image illustrating the distribution of KRT6A and JAK1. Right: Magnified view of the region of interest, highlighting the cytoplasmic colocalization signals. Scale bar = 5 μ m. (E) Diagram of the predicted

99 KRT6A-JAK1 binding region using AlphaFold. (F) HA-JAK1, wildtype
 100 Flag-KRT6A, or mutant (mut) of KRT6A were coexpressed in HEK293T cells
 101 for co-IP assay with anti-Flag beads.

102

103 Supplementary Table S1. The List of Primer Sequences for RT-qPCR

Gene	Species	Forward sequence	Reverse sequence
<i>GAPDH</i>	human	TGTTGCCATCAATGACCCCTT	CTCCACGACGTA CT CAGCG
<i>IL1B</i>	human	AGCTACGAATCTCCGACCAC	CGTTATCCCATGTGTCTGAAGAA
<i>IL6</i>	human	CCTGAACCTTCCAAAGATGGC	TTCACCAGGCAAGTCTCCTCA
<i>TNFa</i>	human	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
<i>CCL20</i>	human	TGCTGTACCAAGAGTTTGCTC	CGCACACAGACA ACTTTTCTTT
<i>CXCL1</i>	human	GCCCAAACCGAAGTCATAGCC	ATCCGCCAGCCTCTATCACA
<i>CXCL11</i>	human	GACGCTGTCTTTGCATAGGC	GGATTTAGGCATCGTTGTCCTTT
<i>KRT6A</i>	human	ATAAGTGTTGTGAACCCCCACC	GCAATTGCAAACAGCGAAGAG
<i>Gapdh</i>	mouse	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA
<i>Il1b</i>	mouse	GCAACTGTTCTGAACTCAACT	ATCTTTTGGGGTCCGTCAACT
<i>Il6</i>	mouse	TAGTCCTTCTACCCCAATTTCC	TTGGTCCTTAGCCACTCCTTC
<i>Tnfa</i>	mouse	CTGAACTTCGGGGTGATCGG	GGCTTGTCACCTCGAATTTTGAGA
<i>Ccl20</i>	mouse	GCCTCTCGTACATACAGACGC	CCAGTTCTGCTTTGGATCAGC
<i>Cxcl1</i>	mouse	CTGGGATTCACCTCAAGAACATC	CAGGGTCAAGGCAAGCCTC
<i>Cxcl11</i>	mouse	GGCTTCCTTATGTTCAAACAGGG	GCCGTTACTCGGGTAAATTACA
<i>Cldn4</i>	mouse	GTCCTGGGAATCTCCTTGGC	TCTGTGCCGTGACGATGTTG

<i>Cldn23</i>	mouse	CCCGACGAGTGGAACACTTC	GGCCAGCGACGAAAAACAC
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104 Supplementary Table S2. The List of Antibody Information

Antibodies	Source	Identifier	Dilution
Anti-human KRT6A	Sigma-Aldrich	HPA061168	WB: 1:1000 IHC: 1:500
Anti-human JAK1	Proteintech	66466-1-Ig	WB: 1:2000
Anti-human pSTAT3	Cell Signaling Technology	9145S	WB: 1:2000 IF: 1:50
Anti-human STAT3	Proteintech	10253-2-AP	WB: 1:2000
Anti-human RNF41	Proteintech	17233-1-AP	WB: 1:500
Anti-FLAG	Thermo Fisher Scientific	MA1-91878	WB: 1:1000
Anti-HA	Cell Signaling Technology	3724S	WB: 1:1000
Anti-HSP90	Proteintech	60318-1-Ig	WB: 1:5000
Anti-LAMIN B1	Proteintech	66095-1-Ig	WB: 1:1000
Anti-GAPDH	Bioworld Technology	AP0066	WB: 1:500
Anti-TUBULIN	Bioworld Technology	BS1482M	WB: 1:1000
Anti-mouse CD4	Thermo Fisher Scientific	14-0042-85	IF: 1:100
Anti-mouse CD31	BD Biosciences	558736	IF: 1:100
Anti-mouse CD31	Cell Signaling Technology	77699	IHC: 1:100

Anti-mouse KRT6A	Abcam	Company-designed	IHC: 1:500
Anti-mouse Ki67	Thermo Fisher Scientific	14-5698-80	IF: 1:500
Donkey anti-Rabbit, Alexa Fluor™594	Thermo Fisher Scientific	A-21207	IF: 1:500
Donkey anti-Rabbit, Alexa Fluor™488	Thermo Fisher Scientific	A-21206	IF: 1:500
Donkey anti-Rat, Alexa Fluor™594	Thermo Fisher Scientific	A-21209	IF: 1:500
Goat Anti-Rabbit IgG H&L	ZSGB-BIO	ZB-2301	WB: 1:20000
Goat Anti-Mouse IgG H&L	ZSGB-BIO	ZB-2305	WB: 1:20000

105