The phosphatase regulator NIPP1 restrains chemokine-driven skin inflammation

Iris Verbinnen[1], Marloes Jonkhout[1], Kifayathullah Liakath-Ali[2], Kathelijne Széker[1], Mónica Ferreira[1], Shannah Boens[1], Raphael Rouget[1], Margareta Nikolic[1], Susan Schlenner[3], Aleyde Van Eynde[1], and Mathieu Bollen[1]

SUPPLEMENTARY INFORMATION

- Supplementary figures S1-S6 and supplementary legends to the figures and Movie S1.
- Supplementary Materials and Methods.
- Supplementary references.
- Supplementary table S1: primers for genotyping.
- Supplementary table S2: antibodies.
- Supplementary table S3: RT-qPCR primers.
- Supplementary table S4: Differentially expressed genes (DEGs) SKOvsCTR (FDR<0.01, two-fold cut-off).
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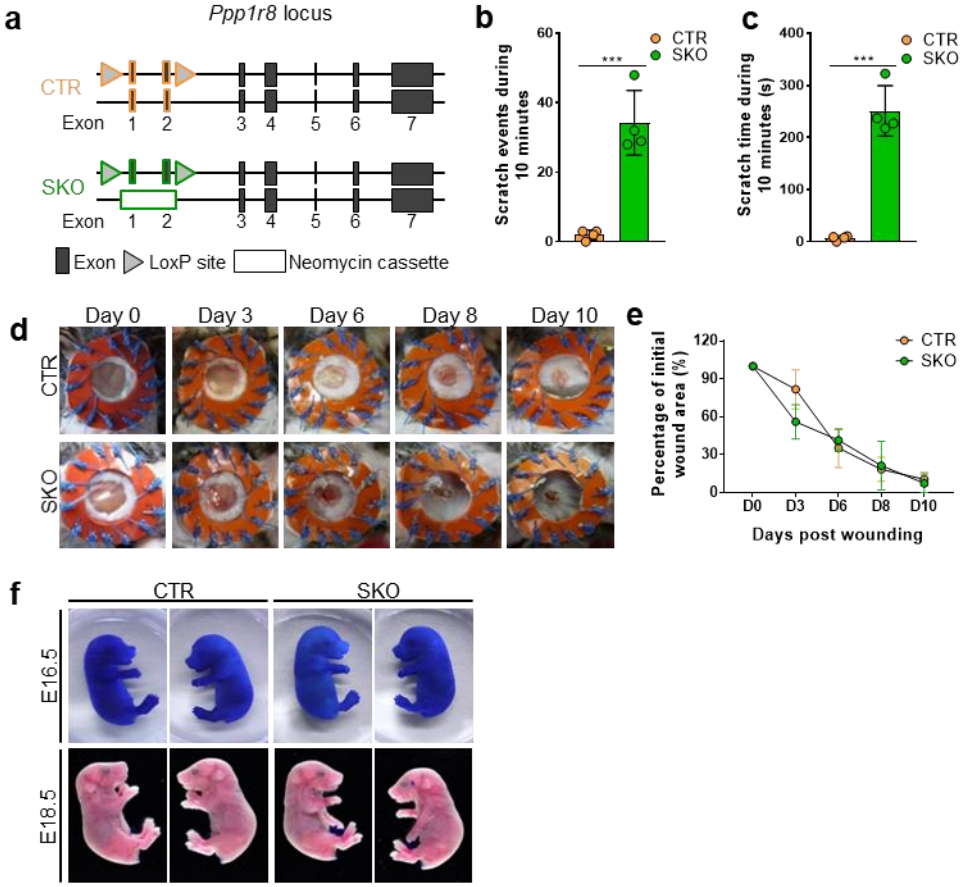
Figure S1

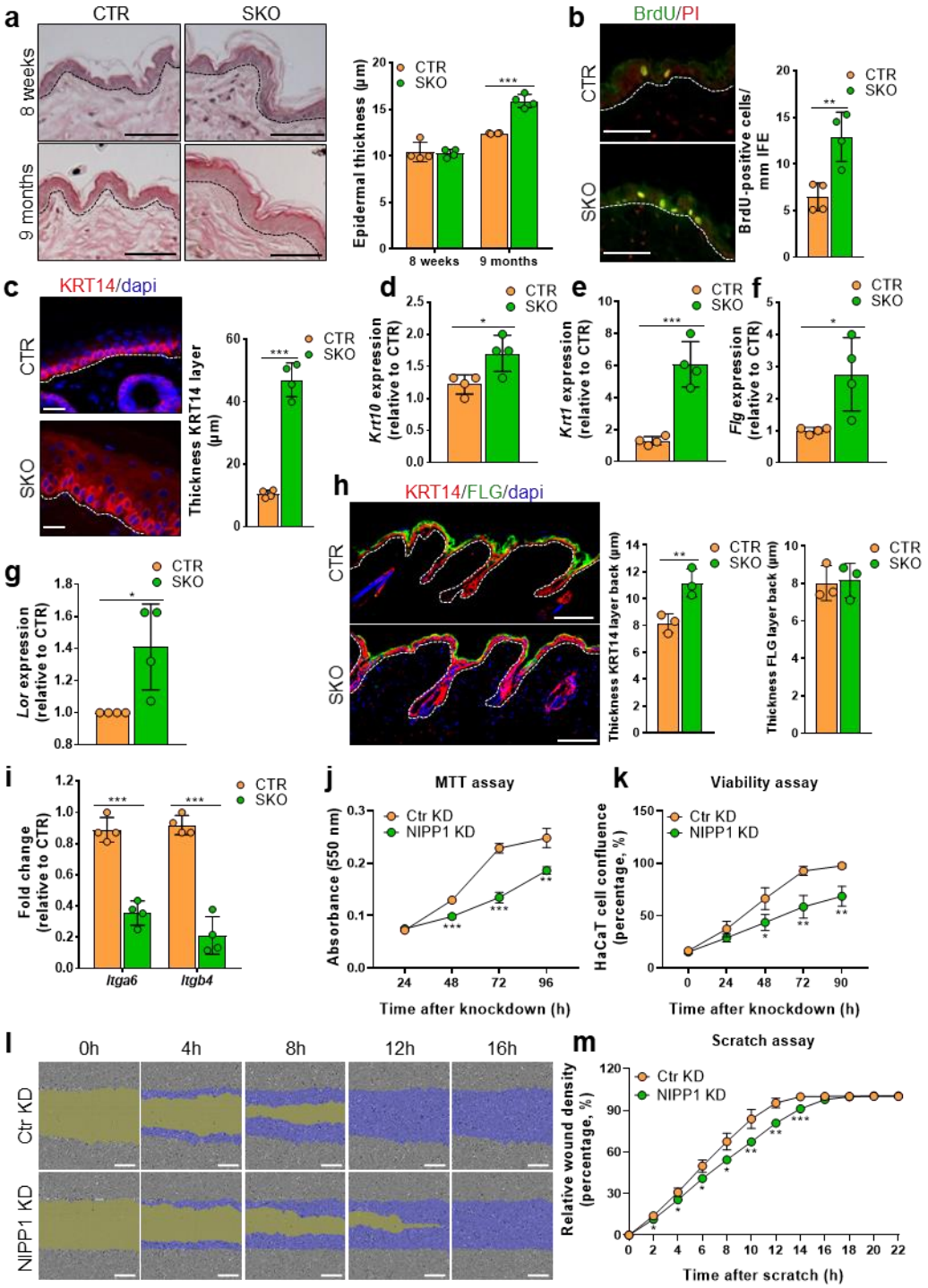


Supplementary Figure 1. Generation and phenotype of skin-specific *Ppp1r8* knockout mice.

(a) Schematic representation of the genotype of keratinocytes of CTR and SKO mice. CTR, Tg(Krt14-Cre)/*Ppp1r8*$^{fl/+}$; SKO, Tg(Krt14-Cre)/ *Ppp1r8*$^{fl/-}$. **(b)** Quantification of scratch events during 10 minutes by CTR and SKO mice of 6-7 months (n=4). **(c)** Quantification of scratch time during 10 minutes by CTR and SKO mice of 6-7 months (n=4). **(d)** Representative pictures of healing of 5-mm punch wounds in CTR and SKO back skin. **(e)** Quantification of wound healing as shown in panel d (5 CTR and 3 SKO). **(f)** Representative images of toluidine blue stainings of CTR and SKO embryos at E16.5 and E18.5.

Bar data are represented as means ± SD. ***, $p<0.001$ (unpaired student's t-test).

Figure S2



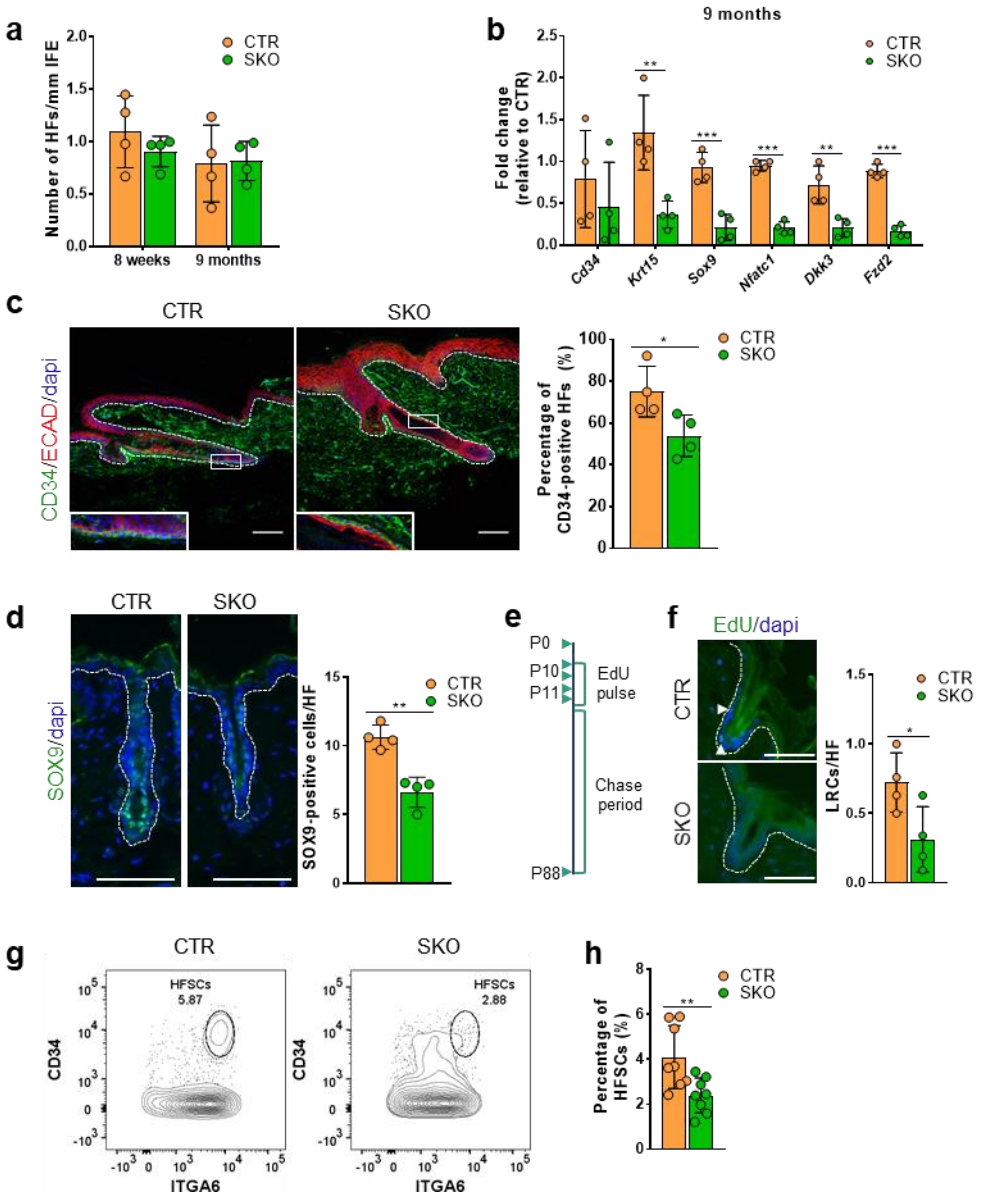
Supplementary Figure 2. Hyperproliferation phenotype in SKOs.

(a) H&E stainings of back skin sections of CTR and SKO mice at the age of 8 weeks and 9 months. Hematoxylin was used as a nuclear counterstain. Scale bars, 50 µm. The bar diagrams

show the quantification of epidermal thickness (n=4). **(b)** Back skin sections from CTRs and SKOs of 8 weeks were immunostained for incorporated BrdU after a 4h pulse labeling. Propidium iodide (PI) was used as a nuclear counterstain. The bar diagrams show the quantification (n=4). **(c)** Tail skin sections from CTRs and SKOs of 8 weeks were immunostained for Keratin-14 (KRT14). Control stainings (i.e. no primary antibody, only secondary antibody) were negative. Dapi was used as a nuclear counterstain. The bar diagram shows the quantification of layer thickness based on the KRT14 immunostainings (n=4). Scale bars, 25 µm. **(d-g)** qRT-PCR analysis of the indicated differentiation markers in tail epidermis from 8-week-old CTR and SKO mice. *Hprt* was used as housekeeping gene for normalization (n=4). **(h)** Back skin sections from CTR and SKO mice of 8 weeks were immunostained for KRT14 and Filaggrin (FLG). Dapi was used as a nuclear counterstain. The bar diagrams show the quantification of layer thickness based on the KRT14- and FLG-immunostainings (indicated in the y-axis) (n=3). Scale bars, 100 µm. **(i)** qRT-PCR of integrins *Itga6* and *Itgb4* in tail epidermis from 8-week-old CTR and SKO mice. *Hprt* was used as housekeeping gene for normalization (n=4). **(j, k)** The growth rate of HaCaT cells after control (Ctr) or NIPP1 knockdown (KD) was determined by MTT assays (**j**) and viability assays (IncuCyte) (**k**) at the indicated time points. Values (points) are represented as means ± SD (n=3). **(l)** The effect of NIPP1 on cell migration was measured by the IncuCyte scratch wound assay. Representative pictures show the initial scratch wound mask (purple) that gets infiltrated by migrated HaCaT cells (yellow scratch wound mask) at the indicated time points after scratching in control and NIPP1-depleted HaCaT cells. **(m)** Wound closure during the IncuCyte scratch wound assay is shown as the relative wound density in percentage at the indicated time points. Each point is the mean of three independent experiments ± SD (n=3).

All bar data are represented as means ± SD. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ (unpaired student's t-test).

Figure S3



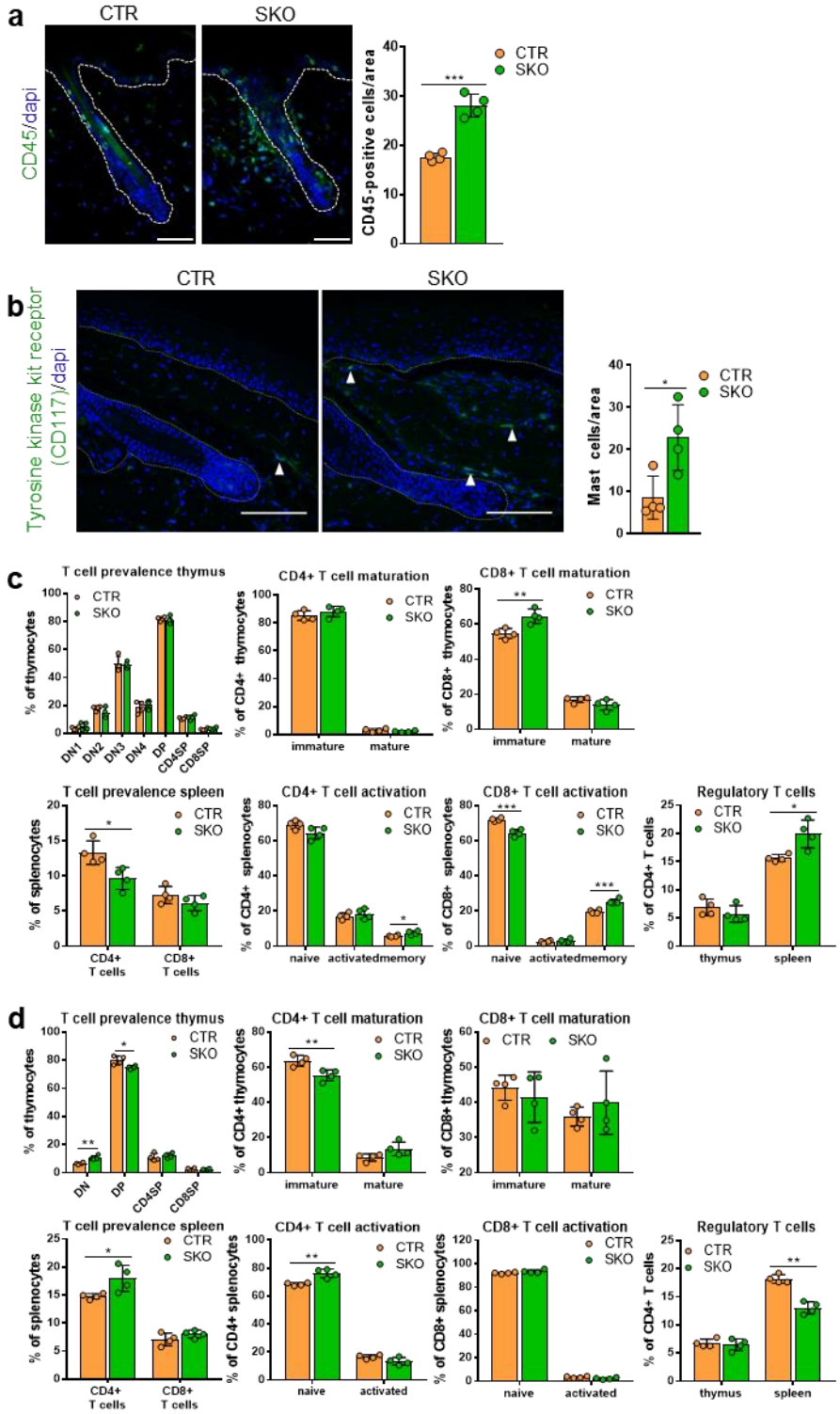
Supplementary Figure 3. The fate of HFSCs in SKOs.

(a) Quantification of the number of hair follicles (HFs) in tail skin from CTR and SKO at 8 weeks and 9 months (n=4). **(b)** qRT-PCR analysis of the indicated HFSC markers in tail epidermis from CTR and SKO mice of 9 months (n=4). *Hprt* was used as housekeeping gene for normalization. **(c)** Tail skin sections from CTR and SKO mice of 10 weeks were immunostained for the HFSC marker CD34 and the adherens junction component E-Cadherin (ECAD). The number of positive cells per HF was quantified (bar diagrams, n=4). Dapi was used for nuclear staining. Scale bars, 200 µm. **(d)** Back skin sections from CTR and SKO mice of 8 weeks were immunostained for the HFSC marker SOX9 and quantified (bar diagrams,

n=4). Dapi was used for nuclear staining. Scale bars, 75 µm. **(e)** Procedure of EdU pulse-chase experiment. 10-days-old-pups were injected intraperitoneally with 5-ethynyl-2'-deoxyuridine (EdU) every 12 hours for a total of 4 injections. Skin samples were collected 77 days after the last injection. **(f)** Back skin sections from EdU-injected CTR and SKO mice were stained for EdU. The bar diagrams show the quantification of the number of EdU-label retaining cells (LRCs) cells per hair follicle (HF). LRCs are indicated by white arrowheads. Dapi was used for nuclear staining. Scale bars, 50 µm. **(g)** Representative flow cytometry profiles of epidermal cells that were isolated from tail skin of 8-week-old CTR and SKO mice and gated for CD34 and ITGA6. **(h)** Quantification (n=8) of the frequency of HFSCs ($CD34^{high}$ $ITGA6^{high}$) by FACS sorting analysis.

Data are represented as means ± SD. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ (unpaired student's t-test).

Figure S4


a
CTR
SKO
CD45/dapi
CD45-positive cells/area
b
Tyrosine kinase kit receptor (CD117)/dapi
Mast cells/area
c
T cell prevalence thymus
% of thymocytes
DN1
DN2
DN3
DN4
DP
CD4SP
CD8SP
CD4+ T cell maturation
% of CD4+ thymocytes
immature
mature
CD8+ T cell maturation
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T cell prevalence spleen
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CD4+ T cell activation
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% of CD4+ splenocytes
naive
activated
CD8+ T cell activation
% of CD8+ splenocytes
Regulatory T cells
% of CD4+ T cells
thymus
spleen

Supplementary Figure 4. Immune response in SKOs.

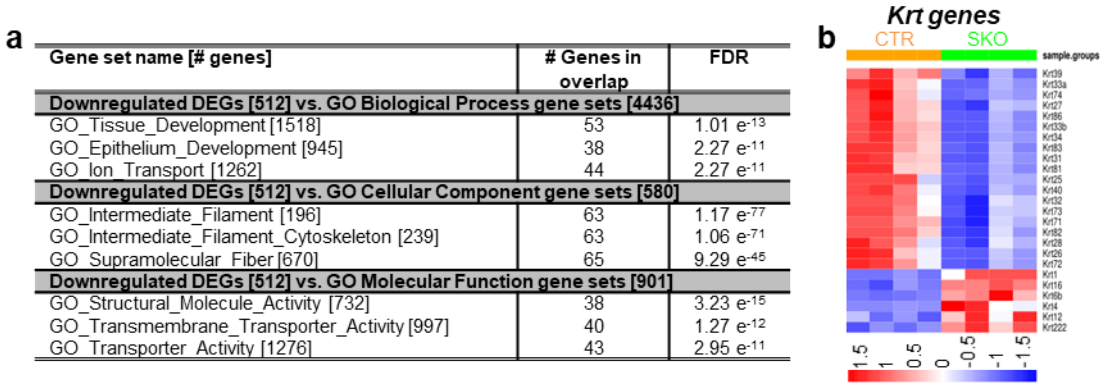
(a) Back-skin sections from CTRs and SKOs of 8 weeks were immunostained for the pan-immune cell marker CD45. Dapi was used as a nuclear counterstain. The bar diagrams show quantifications (n=4). Scale bars, 50 µm. **(b)** Tail-skin sections from CTRs and SKOs of 10 weeks were stained for the mast-cell marker tyrosine kinase kit receptor (CD117) (left panel). Dapi was used as nuclear counterstaining. Area = 100.000 μm^2. For each mouse, 15 pictures were analyzed and the area was extrapolated to 100.000 μm^2. The bar diagrams show the quantification (n=4). Scale bars, 100 µm. **(c)** FACS analysis of T-cell prevalence in the thymus, CD4+ and CD8+ T-cell maturation, T-cell prevalence in the spleen, CD4+ and CD8+ T-cell activation and Regulatory T-cells from CTR and SKO mice of 4 weeks (n=4). **(d)** Idem as in panel (c) but for mice of 8-12 weeks (n=4).

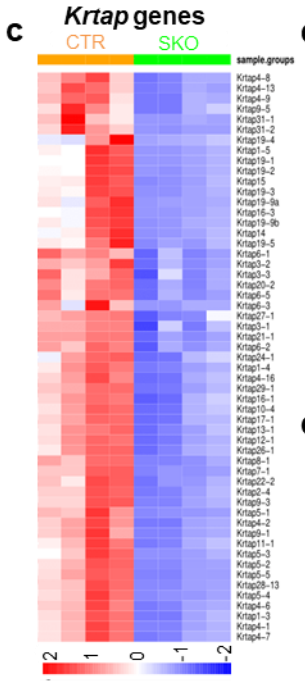
Data are represented as means ± SD. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ (unpaired student's t-test).

Figure S5

a

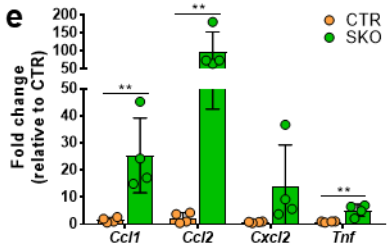
Gene set name [# genes]	# Genes in overlap	FDR
Downregulated DEGs [512] vs. GO Biological Process gene sets [4436]		
GO_Tissue_Development [1518]	53	1.01 e^{-13}
GO_Epithelium_Development [945]	38	2.27 e^{-11}
GO_Ion_Transport [1262]	44	2.27 e^{-11}
Downregulated DEGs [512] vs. GO Cellular Component gene sets [580]		
GO_Intermediate_Filament [196]	63	1.17 e^{-77}
GO_Intermediate_Filament_Cytoskeleton [239]	63	1.06 e^{-71}
GO_Supramolecular_Fiber [670]	65	9.29 e^{-45}
Downregulated DEGs [512] vs. GO Molecular Function gene sets [901]		
GO_Structural_Molecule_Activity [732]	38	3.23 e^{-15}
GO_Transmembrane_Transporter_Activity [997]	40	1.27 e^{-12}
GO_Transporter_Activity [1276]	43	2.95 e^{-11}

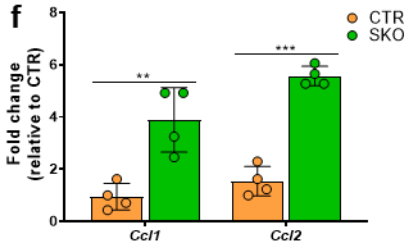


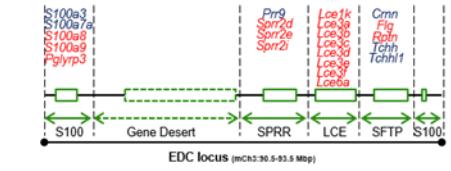


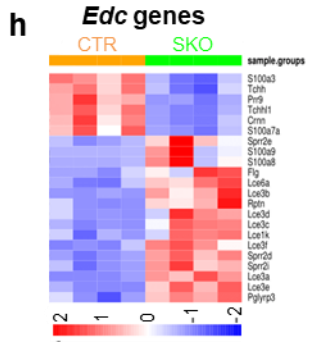
d

Gene set name [# genes]00	# Genes in overlap	FDR
Upregulated DEGs [334] vs. GO Biological Process gene sets [4436]		
GO_Immune_System_Process [1984]	90	6.68 e^{-50}
GO_Immune_Response [1100]	70	2.65 e^{-47}
GO_Defense_Response [1231]	64	1.19 e^{-37}
Upregulated DEGs [334] vs. GO Cellular Component gene sets [580]		
GO_Extracellular_Space [1376]	56	2.31 e^{-27}
GO_Intrinsic_Component_Of_Plasma_Membrane [1649]	51	1.31 e^{-19}
GO_Cell_Surface [757]	30	8.71 e^{-14}
Upregulated DEGs [334] vs. GO Molecular Function gene sets [901]		
GO_Cytokine_Activity [219]	20	4.64 e^{-15}
GO_Receptor_Binding [1476]	43	4.64 e^{-15}
GO_Protein_Complex_Binding [935]	34	1.72 e^{-14}







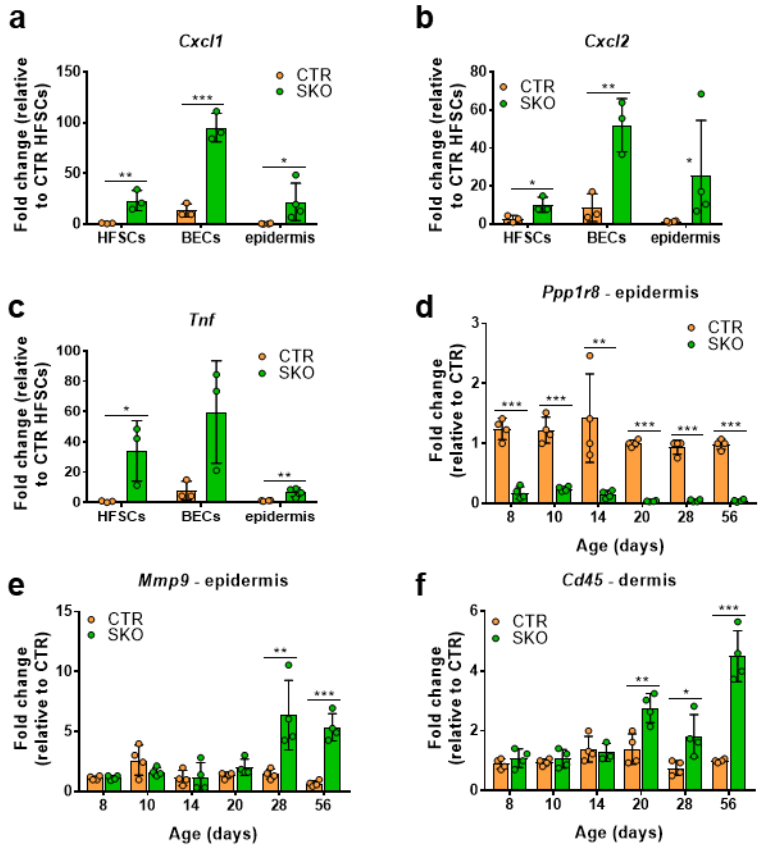


Supplementary Figure 5. Differentially expressed genes in the SKOs.

(a) Gene set enrichment analyses (GSEA) for biological, cellular and molecular function of all downregulated genes (FDR < 0.01, two-fold cut-off) in tail epidermis from CTR and SKO mice of 8 weeks. **(b-c)** Heat map of the significantly (FDR < 0.01, cut-off > 2-fold change) altered *Krt* (b) and *Krtap* (c) genes (n=4). **(d)** Gene set enrichment analyses (GSEA) for biological, cellular and molecular function of all upregulated genes (FDR < 0.01, two-fold cut-off) in tail epidermis from CTR and SKO mice of 8 weeks. **(e, f)** qRT-PCR analysis of the indicated

cytokines in tail (**e**) and back (**f**) epidermis from CTRs and SKOs of 8 weeks. *Hprt* was used as housekeeping gene for normalization. Data are represented as means ± SD (n=4). **, $p<0.01$; ***, $p<0.001$ (unpaired student's t-test). **(g)** Schematic representation of the epidermal-differentiation-complex (EDC) locus in a ~3.1 Mb region of mouse chromosome 3. This locus comprises four tandemly arrayed gene families, i.e. the calcium-binding S100 proteins, the small-proline-rich-proteins (SPRR), the late-cornified-envelope-proteins (LCE) and the S100-fused-type-proteins (SFTP). **(h)** Heat map of the significantly (FDR < 0.01, cut-off > 2-fold change) altered genes in the EDC locus (n=4).

Figure S6



Supplementary Figure 6. Chemokine secretion in the skin of SKOs.
(a-c) qRT-PCR analysis of the indicated cytokines in FACS-purified HFSCs and BECs (n=3) and in total tail epidermis (n=4). *Hprt* was used as a housekeeping gene for normalization. **(d)** qRT-PCR analysis of *Ppp1r8* expression in tail epidermis from CTRs and SKOs of the indicated ages (n=4). *Hprt* was used as a housekeeping gene for normalization. **(e)** qRT-PCR analysis of *Mmp9* expression in tail epidermis of CTR and SKOs of the indicated ages (n=4). *Hprt* was used as a housekeeping gene for normalization. **(f)** qRT-PCR analysis of *CD45* expression in tail dermis of CTR and SKOs of the indicated ages (n=4). *Hprt* was used as a housekeeping gene for normalization.
All bar data are represented as means ± SD. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ (unpaired student's t-test).

Supplementary Movie 1. Scratching behaviour of SKO mice.
Mice were monitored for 10 minutes with a camera and afterwards their scratching behaviour was analyzed. Movie S1 shows 20 seconds of the monitoring of two CTR (orange labels) and two SKO (green labels) mice.

SUPPLEMENTARY MATERIALS AND METHODS

Mouse treatment and experimental design

Mice were housed in a pathogen-free animal facility under standard 12h-light/dark cycles with water and chow *ad libitum*. We used CRE recombinase (CRE) under control of the *Keratin-14* (*Krt14*) promoter to disrupt *Ppp1r8* in keratinocytes from embryonic day (E) 14.5 (Vasioukhin et al. 1999). First, transgenic (Tg) *Krt14-Cre* mice (gift from Walter Birchmeier, Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany) were mated with animals carrying one *Ppp1r8* null allele (*Ppp1r8*$^{+/-}$). Next, Tg*(Krt14-Cre)*/*Ppp1r8*$^{+/-}$ offspring was crossed with mice engineered to have LoxP sites in the promoter region and intron 2 of both *Ppp1r8* alleles (*Ppp1r8*$^{fl/fl}$) and described in (9). Tg*(Krt14-Cre)/Ppp1r8*$^{fl/+}$ and Tg*(Krt14-Cre)/Ppp1r8*$^{fl/-}$ were used as controls (CTR) and skin-specific NIPP1 knockout (SKO) mice, respectively (The generation of *Ppp1r8*$^{fl/fl}$ mice is described in (Boens et al. 2016). DNA used for genotyping was extracted from ear biopsies. PCR primers are described in **Table S1** and the PCR conditions are available on request. Mice were injected with 5'-bromo 2'-deoxyuridine (BrdU) (Sigma-Aldrich) 4h before they were sacrificed. Skin sections were either directly frozen in liquid nitrogen or fixed in PBS containing 4% formaldehyde, or else incubated overnight at 4°C with either 10 mg/ml dispase (Sigma-Aldrich) or 2.5 mg/ml trypsin (Sigma-Aldrich) when separation of epidermis was required. All experimental protocols were in accordance with and approved by the Guide of Care of Experimental Animals of the KU Leuven Ethical Committee (license number 053/2018).

Skin-barrier assays

For embryo whole-mount dye-penetration assays, embryos were dissected at E16.5 or E18.5, sacrificed, rinsed in PBS and quickly dehydrated and rehydrated through immersion in consecutively 25, 50, 75, 100, 75, 50 and 25% methanol, and subsequently rinsed in PBS. Staining was performed by immersion of the embryos in 0.1% toluidine blue (Fluka) in PBS

for 2 minutes. The embryos were destained in PBS at pH 7.4. The barrier function was evaluated based on the degree of dye penetration (Hardman et al. 1998). Transepidermal water loss (TEWL) was measured with the DermaLab® device (Cortex Technology). Briefly, the back skin of 8-week-old mice was shaved one day before measurements were started. TEWL measurements were always performed in the afternoon and in the same assessment room without air circulation. Room temperature (mean = 20.6°C, SD = 0.4, n=3) and humidity (mean = 62.1%, SD = 4.3; n=3) were registered before recording. For each mouse, three regions were measured in triplicate and the mean value for each region was calculated.

Assessment of scratching behaviour

Mice were monitored for 10 minutes with a camera and afterwards the number of scratch events during this time period was counted. The total scratch time during 10 minutes was also measured.

Wound-healing assay

Mice were anaesthetized with isoflurane and hair on their back skin was removed. Mice were taped on their ventral side on a heating pad. The area between the shoulders was desinfected with 2% iodine-alcohol and a piece of skin was removed with the 5-mm Stiefel biopsy punch (05.SF004.11/08). Histoacryl (Braun) was put on one side of an 8-mm silicone ring (Thermo Fisher Scientific) to tape the ring to the skin around the skin wound, and the ring was sutured to the skin using 6.0 prolene. Next, a drop of 0.9% NaCl was put in the wound to prevent it from drying out and the wound was covered with tegaderm film (Health Care). Mice were housed individually during the course of the experiment. On days 3, 6, 8 and 10 after wounding, mice were sedated with isoflurane and the tegaderm film was removed in order to take a picture of the wound. One phase exponential decay modelling in GraphPad Prism version 7 was used to compare the wound healing process between CTR and SKO mice.

EdU proliferation assay

Pups of 10 days were intraperitoneally injected with 100 µl of 6.25 mg/ml 5-ethynyl-2'-deoxyuridine (EdU) every 12 hours for a total of 4 injections and imaged using the Click-iT® EdU Alexa Fluor® 488 Imaging Kit (Thermo Fisher Scientific). Skin samples were collected 77 days after the last injection. Epidermal tail sections were prepared for wholemount staining as described previously (Liakath-Ali et al. 2014). Back skin sections were fixed in PBS containing 4% formaldehyde, embedded in paraffin and sections of 5 µm were stained. EdU detection was performed as described by the manufacturer and by Mead *et al*. 2014 (Mead and Lefebvre 2014). Microscopy was carried out using a Leica DMI 4000B microscope and images were processed with ImageJ software (National Institute of Health).

Dexamethasone treatment

Mice were intraperitoneally injected daily, for 15 consecutive days, with 4 mg/kg rapidexon/dexamethasone (Eurovet Animal Health, Dechra) or vehicle (saline). After this period, mice were sacrificed and skin tissue was used for immunohistochemical and qRT-PCR analysis.

Flow cytometry

To analyze HFSCs and BECs, flow cytometry analysis was performed as described previously (Jensen et al. 2010; Moestrup et al. 2017), with some minor modifications. Briefly, tail skin pieces were incubated overnight at 4°C with 10 mg/ml dispase (Sigma-Aldrich), and subsequently for 1h at 37°C in 2.5 mg/ml trypsin (Gibco). After separating the epidermis from the underlying dermis, single cells from the epidermis were released into suspension by breaking tissue fragments in 2.5 mg/ml trypsin (Gibco) and passing through 70-µm cell strainers (VWR international). Next, cells were counted and pelleted at 500 *g* for 8 minutes. Cells were stained with fluorescently labeled antibodies (APC-ITGA6, PE-CD34, PE/Cy7-CD45, PE/Cy7-CD31) for 1h at 0°C , washed twice with FACS buffer (PBS supplemented with 0.1% BSA) and analyzed in a BD FACSCanto II or sorted in a BD FACSAriaII (FACS core

facility, KU Leuven). Compensation was achieved by using UltraComp eBeads (Thermo Fisher Scientific). Expression of cell surface markers was analyzed on living cells after exclusion of cell doublets, CD45/CD31-positive cells and dead cells using propidium iodide (Thermo Fisher Scientific). The purity of the sorted cell populations was verified by post-sort analysis.

To analyze immune cells in the skin, flow cytometry was performed as described previously (Lay et al. 2018), with some minor adaptations. Briefly, tail skin was minced into small pieces and incubated for 75 min at 37°C in RPMI-1640 medium with L-glutamine and sodium bicarbonate (Sigma-Aldrich), supplemented with 5% FBS, 120 µg/ml Liberase TM (Roche) and 600 µg/ml DNaseI (Roche). Washing buffer containing HBSS (Gibco) and 20% FCS was added to stop the digestion. The skin pieces were squeezed through a 70-µm cell strainer (VWR international), counted and pelleted at 500 *g* for 8 minutes. Cells were stained with antibodies, including AF488-CD45, BV711-MHCII, BV605-CD11c, PE/Cy7-CD64, BUV395-CD11b, PE-CD207. Next, cells were fixed using the eBioscience Foxp3 fixation/permeabilization buffer (Thermo Fisher Scientific) and resuspended in PBS supplemented with 2.5% FCS. Dead cells were excluded by using the eF780 fixable viability dye (Thermo Fisher Scientific). Compensation was achieved by using UltraComp eBeads (Thermo Fisher Scientific). Immune cells were analysed with the BD FACSymphony A3 (FACS core facility, KU Leuven).

To analyze T cell maturation and activation by flow cytometry, thymi and spleens of 4-week-old and 8-12-week-old CTR or SKO mice were homogenized and spleens underwent red blood cell lysis. After blocking with ChromPure mouse IgG (Jackson ImmunoResearch), one half of the thymocytes were stained with CD4-PE, CD8-Fitc, CD24-PerCP-eFluor710, Qa2-biotin, Foxp3-APC and Streptavidin-BV421. Mature single positive (SP) cells were defined as CD4SP or CD8SP CD24loQa-2hi, immature SP cells were defined as CD24hiQa2lo, regulatory T-cells were identified as CD8-CD4+Foxp3+. The other half was depleted of CD8-SP cells and double positive (DP) cells using CD8-biotin and Streptavidin magnetic beads (Dynabeads

M280, Invitrogen) to enrich for double negative (DN) cells. Enriched cells were stained for Lineage-Fitc (CD4, CD11b, Gr1, CD19, CD49b, NK1.1, TCRgd, Ter119, Streptavidin-Fitc), CD25-PerCP-Cy5.5 and CD44-PE. Lineage-negative developmental stages were defined as follows: DN1 CD25-CD44+, DN2 CD25+CD44+, DN3 CD25+CD44-, CD4 CD25-CD44-. Total splenocytes were stained for CD4-Fitc, CD8-APC-Cy7, CD44-biotin/Streptavidin-BV421, CD62L-PE and Foxp3-APC. Naïve CD4 and CD8 T cells were defined as CD62L+CD44-/lo, activated CD4 and CD8 T cells as CD62L-CD44hi, and effector-memory CD4 and CD8 T cells as CD62L+CD44hi. Data of all flow cytometry experiments were analyzed using FlowJo software. The antibodies for flow cytometry are described in **Table S2**.

RNA-sequencing

Total RNA was isolated from 40 mg of snap-frozen tail epidermis from 4 CTR and 4 SKO mice (age of 8 weeks), using the GenElute^{TM} Mammalian Total RNA Miniprep kit (Sigma-aldrich). RNA integrity of the samples used for RNA sequencing was assessed using a Bioanalyser 2100 (Agilent). Library preparation, sequencing and statistical analysis of the RNA sequencing data were performed by the VIB Nucleomics Core (www.nucleomics.be), according to their standard protocols, as detailed in (Ferreira et al. 2017). All gene expression data are available at GEO under accession number GSE116844 https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE116844.

Histological and immunohistochemical analysis

Skin tissue was immediately fixed in PBS containing 4% formaldehyde, and embedded in paraffin at the Histology & Imaging facility (Vesalius Research Center, KU Leuven). Skin sections of 5 µm were stained with hematoxylin and eosin (H&E). For cryosections, skin tissue was fixed in PBS containing 4% formaldehyde for 20 minutes, washed twice with ammoniumchloride and incubated with 30% sucrose overnight at 4°C. The next day, the tissue was embedded in Tissue-Tek® O.C.T. Compound (Sakura). Skin sections of 10 µm were cut

with a Cryostat NX70 at the Histology & Imaging facility (Vesalius Research Center, KU Leuven). Wholemount stainings on tail skin section were prepared and performed as described previously (Liakath-Ali et al. 2014). The antibodies used for immunohistochemistry are described in **Table S2.** Microscopy was carried out using a Nikon A1R confocal, a Leica DMI 4000B, or a Leica DMBL, and images were processed with NIS Elements (Nikon Instruments) or Leica MM AF software or Leica IM50 Image Manager, respectively. Images were analyzed using ImageJ (National Institute of Health) or Icy software (Institut Pasteur, Paris, France).

Protein extraction

Epidermal lysates were made in a modified RIPA buffer containing 50 mM Tris-HCl at pH 7.5, 0.3 M NaCl, 0.5% Triton X-100, 0.2% Sodium dodecyl sulfate (SDS), 1 mM EDTA, and 0.2% sodium deoxycholate. The buffer was supplemented with protease inhibitors (1 mM phenylmethanesulfonyl fluoride, 1 mM benzamidine, 5 µM leupeptin) and protein phosphatase inhibitors (25 mM sodium fluoride, 1 mM orthovanadate). Samples were first incubated for 20 minutes on ice, and then homogenized with both a polytron blender and a Potter-Elvehjem homogenizer. Samples were incubated for 20 minutes on ice and centrifuged for 3 minutes at 11,000 *g*. The supernatant was collected and the pellet was resuspended in a buffer containing 50 mM Tris-HCl at pH 7.5, supplemented with 1.5 mM $CaCl_2$ and protease inhibitors (1 mM phenylmethanesulfonyl fluoride, 1 mM benzamidine, 5 µM leupeptin) and protein phosphatase inhibitors (25 mM sodium fluoride, 2 mM orthovanadate), and treated with 90 units of micrococcal nuclease for 30 minutes at 37°C. These lysates were centrifuged for 5 minutes at 1,700 *g* and the supernatants were retained. Both supernatant fractions were pooled and processed for SDS-PAGE and immunoblotting. Proteins were blotted on polyvinylidene fluoride membranes (GE Healthcare) and probed with various antibodies (**Table S2**). Immunoblots were visualized using ECL reagent (Perkin Elmer, Life Sciences) in the

ImageQuant LAS4000 imaging system (GE Healthcare) and were quantified using ImageQuant TL Software (GE Healthcare).

Cell culture

HaCaT cells were cultured in DMEM medium with 4.5 g/L glucose and 2 mM L-glutamine (Sigma-Aldrich), supplemented with 1 mM sodium pyruvate (Sigma-Aldrich), 10% FCS and 1% Penicillin/Streptomycin. SiRNA duplexes against human NIPP1 (stealth siRNA NIPP1, sequence: GGAACCUCACAAGCCUCAGCAAAUU) and the non-targeting control (stealth control, scrambled version of stealth siRNA NIPP1, sequence: GGAACUCGAACCUCCACGAACAAUU) were purchased from Thermo Fisher Scientific. The siRNA transfections were performed using RNAiMAX transfection reagent (Thermo Fisher Scientific). For MTT assays, 20,000 HaCaT cells were seeded in each well of a 48-well plate and knockdowns were performed as described above. 0.4 mg/ml of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each well after 24h, 48h, 72h and 96h knockdown. After 1h of incubation, the medium was removed and the purple crystals were dissolved in DMSO. The absorbance was measured at 550 nm. For viability assays, 12,000 HaCaT cells were seeded into 96-well plates and knockdowns were performed as described above. Cell confluence was automatically monitored by the IncuCyte (Essen BioScience) for 90h. For the IncuCyte scratch wound assay, HaCaT cells (60,000 cells/well) were seeded onto collagen-I-coated 96-well ImageLock tissue culture plates (Essen BioScience), knockdowns were performed as described above and the plates were incubated in a standard CO_2 incubator for 24h to form cell monolayers. Wounds were made with the 96-well WoundMaker (Essen BioScience). The wounded cells were washed twice with culture medium to remove the detached cells and then 100µl of medium was added per well. Images of the wounds were automatically acquired within the CO_2 incubator by IncuCyte zoom software (Essen BioScience). Kinetic updates were taken at 2h-intervals for 96h. The data were analysed

with respect to wound confluence and calculated by using the IncuCyte software package (Essen BioScience).

Quantitative Reverse Transcriptase (qRT) - PCR

Total RNA was isolated from snap-frozen mouse epidermis, dermis, FACS-purified BECs or from HaCaT cells (stored at -80°C) using the Genelute Mammalian Total RNA Miniprep kit (Sigma-Aldrich). Total RNA from snap-frozen FACS-purified HFSCs (stored at -80°C) was isolated using the RNeasy Plus Micro Kit (Qiagen). Complementary DNA (cDNA) was synthesized from 200 ng (minimum) and 2 µg (maximum) of total RNA using oligo (dT) primers (Sigma-Aldrich), RevertAid Premium Reverse Transcriptase and RiboLock RNase inhibitor enzymes (Fermentas). 1.2% of the cDNA was PCR-amplified in duplicate using SYBR Green qPCR Mix (Invitrogen) and a Rotorgene detection system (Corbett Research) (Boens et al. 2016). To determine the relative amount of target in different samples, all values were normalized to the housekeeping gene *Hprt* (Hypoxanthine-guanine phosphoribosyltransferase). All used qRT-PCR primers can be found in **Table S3**.

Data analysis

The results are expressed as means ± standard deviation (SD) and analyzed with the unpaired Student t-test. The wound healing process between CTR and SKO mice was compared by one phase exponential decay modelling and the difference between the fit of the curves was determined by the Mann-Whitney test. Statistical analysis was performed in GraphPad Prism version 7 (GraphPad software, Inc). All data from qPCR analysis and Western blot analysis are shown as a fold change, i.e. SKO values relative to one CTR. The value of the other CTR samples was also expressed relative to this CTR value to show the variation between the CTR samples. For the analysis of the ITGA6 and ITGB4 staining, intensity values of CTR and SKO samples were calculated with Icy. The mean value of all CTR intensity values was calculated. Next, all intensity values of CTR and SKO samples were normalized to this ‘mean CTR

intensity value'. In both wholemount sections (ITGA6) and 2D sections (ITGB4) the intensity values in IFE were quantified.

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SUPPLEMENTARY TABLE S1: primers for genotyping.

Target	Sense Primer	Antisense Primer
K14-CRE recombinase	CTTGCGAACCTCATCACTCG	AGGGATCTGATCGGGAGTTG
NIPP1 fl/fl - Neodeletion - LoxP	CCACCCTCTCCTTTACTTTGTCTTC CTTACAAGGAGTGGTATTCGA	GGAGAGGAGTAATGAGGAGTTGTG ACTGTCTAGCAGGGCATAGTGTTG
NIPP1 knockout	CCTCAGCAGATAGCCCACGG	CGCATCGCCTTCTACGCCTTCTTGAC

SUPPLEMENTARY TABLE S2: antibodies.

Target protein	Company	Application
CD34-PE (clone RAM 34)	BD Pharmingen	FC
ITGA6-APC (clone GoH3)	Thermo Fisher Scientific	FC
CD45-PE/Cy7 (clone 30-F11)	BioLegend	FC
CD31-PE/Cy7 (clone 390)	BD Pharmingen	FC
CD45-AF488 (clone 30-F11)	BioLegend	FC
MHCII (I-A/I-E)-BV711 (clone M5/114.15.2)	BioLegend	FC
CD11c-BV605 (clone N418)	BioLegend	FC
CD64-PE/Cy7 (clone X54-5/7.1)	BioLegend	FC
CD11b-BUV395 (BD Horizon) (clone M1/70)	BD Biosciences	FC
CD207-PE (clone 4C7)	BioLegend	FC
CD4-Fitc	eBioscience	FC
CD4-PE (clone GK1.1)	eBioscience	FC
CD8-Fitc	eBioscience	FC
CD8-APC-eFluor780 (clone 53-6.7)	eBioscience	FC
CD11b (clone M2/70)	eBioscience	FC
Gr1 (clone RB6-8C5)	eBioscience	FC
CD19 (clone 1D3)	eBioscience	FC
CD49b (clone DX5)	eBioscience	FC
NK1.1 (clone PK136)	eBioscience	FC
TCRgd (clone GL3)	eBioscience	FC
Ter119 (clone Ter-119)	eBioscience	FC
Streptavidin-Fitc	eBioscience	FC
CD62L-PE (clone MEL-14)	eBioscience	FC
CD44-PE	eBioscience	FC
CD44-biotin (clone IM7)	eBioscience	FC
Foxp3-APC (clone FJK-16s)	eBioscience	FC
CD24-PerCP-eFluor710 (clone M1/69)	eBioscience	FC
CD25-PerCP-Cy5.5 (clone PC-61.5)	eBioscience	FC
Streptavidin-BV421	BioLegend	FC
Qa2-biotin (clone 1-1-2)	BD Pharmingen	FC
NIPP1	Sigma-Aldrich	IHC

Ki67 (clone SP6)	Abcam	IHC
H3S10ph (clone MC463)	Upstate Biotechnology	IHC
BrdU	Dako	IHC
Keratin-14 (clone LL002)	Abcam	IHC
Keratin-10 (clone Poly19054)	BioLegend	IHC
Keratin-1 (clone Poly19056)	BioLegend	IHC
Filaggrin	Santa Cruz Biotechnology	IHC
Loricrin (clone Poly19051)	BioLegend	IHC
Integrin-α6-FITC (clone GoH3)	BioLegend	Wholemount
Integrin-β4 (clone 346-11A)	BD Pharmingen	IHC
Directly conjugated (Alexa Fluor 555) Keratin-14 (clone LL002)	Lab Fiona Watt (King's College London)	Wholemount
Directly conjugated (Alexa Fluor 488) Keratin-15 (clone LHK-15)	Lab Fiona Watt (King's College London)	Wholemount
FASN (clone G-11)	Santa Cruz Biotechnology	Wholemount
Ki67 (NCL-Ki67p)	Novacastra	Wholemount
CD45 (clone 30-F11)	BD Biosciences	IHC
Sox9	Millipore	IHC
CD34 (clone RAM34)	Thermo Fisher Scientific	IHC
E-Cadherin (clone 24E10)	Cell Signaling Technology	IHC
CD117 (clone ACK2)	Thermo Fisher Scientific	IHC
Alexa Fluor 488 goat anti-rabbit IgG (H+L)	Invitrogen	IHC
Alexa Fluor 488 donkey anti-mouse IgG (H+L)	Invitrogen	IHC
Alexa Fluor 568 goat anti-mouse IgG (H+L)	Invitrogen	IHC
Goat anti-Rat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488	Invitrogen	IHC
Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 546	Invitrogen	IHC
Swine anti-rabbit HRP	Dako	IHC + WB
Anti-mouse HRP	Dako	IHC + WB
NIPP1	Van Eynde et al. 2004	WB
GAPDH	Cell Signaling Technology	WB

FC: flow cytometry; IF: immunohistochemistry; WB: western blot

SUPPLEMENTARY TABLE S3: RT-qPCR primers.

Gene	Sense Primer	Antisense Primer
Ccl1	CCGTGTGGATACAGGATGTT	GAAGCTCTTTCTTCAAGGTGTTC
Ccl2	CTGGAGCATCCACGTGTT	GCCTACTCATTGGGATCATCTT
CCL2	TCATAGCAGCCACCTTCATTC	CTCTGCACTGAGATCTTCCTATTG
CCL20	CTCCTGGCTGCTTTGATGT	GGATGAAGAATACGGTCTGTGTAT
CCL22	GACTGCACTCCTGGTTGTC	CAGACGCTGTCTTCCATGTT
CCL7	CTCTGCAGCACTTCTGTGT	AAATCTGTAGCAGCAGGTAGTT
Cd34	ACCAGCCATCTCAGAGACTAT	GTAGTAGGCAGTATGCCAGTTG
Cd45	TGCCTATGTCAATGGGAAGATT	GGCCATTAGTTTCATAAGGAGGA
Cxcl1	TTCACCTCAAGAACATCCAGAG	AAGCCTCGCGACCATTC
CXCL1	GTGGCACTGCTGCTCCT	AGGGTCTGCAAGCACTGG
CXCL10	GCTGCCTTATCTTTCTGACTCT	GACCTTGGATTAACAGGTTGATTAC
CXCL16	CCCATGGGTTCAGGAATTGA	GGCTGGTAGGAAGTAAATGCT
Cxcl2	TCAAGAACATCCAGAGCTTGAG	CTTCAGGGTCAAGGCAAACT
Dkk3	CCAGTTCTCCAGCTTCAAGTA	CCACAGCACTCACTGTCTC
Flg	AGGAGGAAGAAACACTGAGCA	AGTTTGTCATCGTGGTCCAC
Fzd2	TGCCGTCCTATCTCAGCTATAA	CCTCTTGCGAGAAGAACATAGAG
Hprt	CTGGTGAAAAGGACCTCTCG	TGAAGTACATTATAGTCAAGGGCA
HPRT	TGACACTGGCAAAACAATGCA	GGTCCTTTTCACCAGCAAGCT
Itga6	AAGGTTTGGAGCAGATTGTTT	TTTCAGGAAGTTCCCGTTTCT
Itgb1	CAGCAACGCATATCTGGAAAC	TACATTCCTCCAGCCAATCAG
Itgb4	GGATAATACAGCACACGGACA	AGTAGCTTCACCTGCAACTC
Krt1	GACACCACAACCCGGACCCAAAACTTAG	ATACTGGGCCTTGACTTCCGAGATGATG
Krt10	GGAGGGTAAAATCAAGGAGTGGTA	TCAATCTGCAGCAGCACGTT
Krt15	GCTCAGAACCAGGAGTACAAC	AATACCAGCCATCTTAGCATC
Lor	TCACTCATCTTCCCTGGTGCTT	GTCTTTCCACAACCCACAGGA
Mmp9	CAGCCAACTATGACCAGGATAA	TCGCTGGTACAGGAAGAGTA
Nfatc1	GGCGGGAAGAAGATGGTGCTGTC	TGGTTGCGGAAAGGTGGTATCTCA
Ppp1r8	TACATCTGGATGTGGTGAAAGG	GGTCGATAGTGAAGTCACACAG

PPP1R8	TACACACGGCACTTTCTTGG	CTTGTTGTGGGCAGTGTTGA
S100a8	AAATCACCATGCCCTCTACAA	CACTATTGATGTCCAATTCTCTG AAC
Sox9	CTCTGGAGGCTGCTGAAC	CGCTTGTCCGTTCTTCAC
Tnf	TCTTCTGTCTACTGAACTTCG	GGCCATAGAACTGATGAGAG

SUPPLEMENTARY TABLE S4: Differentially expressed genes (DEGs) SKOvsCTR (FDR<0.01, two-fold cut-off).

Gene name	SKOvsCTR : logFC	SKOvsCTR : FDR
Ccl2	5.569476383	2.4143E-32
Cdkn2a	5.323965457	3.00611E-12
Stfa1	5.300138712	2.58015E-05
Defb5	5.182281401	1.72299E-14
Ccl1	4.96704325	2.31247E-33
S100a9	4.622518139	1.43652E-10
Ccl20	4.228922878	4.66147E-23
Gm5416	4.181110723	1.11493E-10
S100a8	4.174235752	5.45686E-11
Pglyrp2	4.100906903	5.13833E-45
Tslp	4.041658227	7.9062E-12
Krt6b	4.034168573	9.65337E-27
Ascl3	3.98618632	7.65471E-11
Krt4	3.675455067	6.83376E-12
Ch25h	3.599877533	9.73667E-06
Lce3b	3.480519056	1.73387E-10
Tas1r2	3.450724354	6.71019E-14
Blk	3.385207475	9.2625E-09
Lce3a	3.346668465	1.95337E-14
Gm5478	3.336928673	0.007283311
Axdnd1	3.276457843	1.82696E-14
B3gnt3	3.220092241	0.000611605
Cxcl10	3.2093752	1.16146E-08
Tnfsf4	3.157810331	8.93336E-05
Rgs4	3.124274678	0.000265427
Icos	3.025441396	0.000115095
Cxcl9	2.988683416	0.000689781
2610528A11Rik	2.985216942	1.20186E-17
Stfa2	2.940976351	1.34879E-10
Il2rg	2.924128947	5.27519E-08
5830411N06Rik	2.918900573	1.60793E-11
Ltb	2.917122347	7.03577E-06
Ccr2	2.906344841	2.25655E-08
Epb42	2.879079741	8.41099E-07
Gbp2	2.861369161	1.03382E-06
Cxcl1	2.837231096	7.51794E-07
Il18r1	2.821486218	1.32664E-17
Ccl7	2.818406405	0.000224406
Cyp7b1	2.791610531	3.23083E-15
Ppp1r1c	2.790473732	1.1543E-05
Cd247	2.7702066	6.69687E-06
Lce3e	2.694939684	9.33271E-11

Slit1	2.67632118	1.90976E-20
Rac2	2.667771175	0.000117646
Igsf6	2.640476991	1.96569E-05
Usp18	2.629431714	0.005030302
Cd3e	2.608574217	1.26872E-05
Ctsk	2.583007451	0.00012796
Slc38a5	2.57975073	0.001614665
Stfa3	2.57083166	1.959E-06
Gja4	2.569933305	1.40419E-20
Uba7	2.550012073	2.18727E-07
Lrrc9	2.528480774	1.19267E-06
Ambp	2.485060346	1.85096E-07
Defb3	2.441766769	0.002668362
Lce3f	2.440722527	1.4021E-09
Il18rap	2.43188571	6.72608E-06
Lce3d	2.388781333	1.12703E-05
Scimp	2.386576715	8.88112E-05
Ttc34	2.382470284	4.74269E-07
Pkd2l1	2.372923628	1.50725E-10
Lrrn4cl	2.369208318	5.06046E-08
Tnf	2.364621827	2.13605E-06
Adgrg3	2.341667611	1.02947E-17
Slc16a3	2.331840536	3.83735E-22
Sash3	2.310013073	0.000365201
Pmaip1	2.270588654	7.92366E-09
Ankk1	2.259416444	6.43301E-06
Fxyd1	2.259224343	0.002112139
Tmem132b	2.246987296	2.49969E-07
1700012P22Rik	2.235049877	1.66028E-18
Lax1	2.231451207	2.10887E-20
Mmp9	2.21669885	2.68206E-10
Sult4a1	2.189872386	1.44229E-06
Slc2a6	2.163465871	5.59804E-05
Pld4	2.142267156	0.000216944
Lpo	2.129146636	0.000473135
Pik3r5	2.123616919	9.82959E-05
Guca2b	2.116846777	2.82447E-08
Lcn2	2.114326884	3.1714E-10
Mfrp	2.107802037	1.74864E-05
Hgfac	2.071972951	0.008151816
Slpi	2.062517659	5.56526E-12
Gm9905	2.039170455	1.05286E-10
Ankmy1	2.037680573	2.28595E-07
Casp4	2.037305091	0.000272302

Artn	2.033294683	2.40136E-07
Casp12	2.031322192	0.002545135
Mx1	1.989569898	9.55259E-05
Apol8	1.986408619	1.3239E-08
Rgs18	1.980949482	1.26271E-05
Prl2c5	1.971858905	0.001020909
Zfp423	1.970191747	0.000683254
Ecscr	1.962364308	0.000623455
Cyp17a1	1.961045691	7.08457E-34
Sp8	1.960386478	4.17535E-06
Sprr2e	1.940237644	6.43301E-06
Chga	1.940190275	3.60766E-09
Gpr35	1.932102412	4.93457E-26
Spink14	1.914599782	7.27657E-05
Arl9	1.89873438	0.001470661
Chil1	1.892729004	9.6825E-13
Vsnl1	1.886332444	6.53537E-06
Dlgap1	1.879269433	1.76319E-10
0610009L18Rik	1.87490405	4.73939E-10
Lif	1.870071066	4.10946E-07
Il7r	1.867356535	1.58689E-08
Scd3	1.851224436	1.01996E-10
Iyd	1.837991722	0.000664947
Phf11d	1.82046899	0.000498488
Gstm6	1.818233335	4.13413E-07
Serpinb6e	1.814838497	0.006523674
Fetub	1.810969395	9.01899E-16
Igfbp6	1.809873893	7.83983E-09
Cxcr6	1.801272371	1.44983E-05
Rptn	1.793000091	2.61795E-07
Lce3c	1.766498022	1.81088E-13
C1qtnf1	1.737118642	2.49969E-07
Dnmt3l	1.733529328	0.007214623
Prr22	1.732985188	5.40831E-05
Gsta4	1.721945611	0.000788107
Dock2	1.719123784	0.000113138
Nlrc5	1.710007555	9.31974E-21
Serpina3j	1.682516956	0.005880725
Gm9958	1.663378954	2.89553E-11
Fam105a	1.644134291	2.44031E-12
Igtp	1.643225564	1.33129E-07
Tekt2	1.637897071	3.19803E-10
Tnnt2	1.633166878	1.06004E-07
Cd52	1.626022278	4.91084E-06

Avil	1.607453913	1.76872E-06
Tmem116	1.606229948	2.65307E-06
Sprr2d	1.581103301	1.87372E-22
Pla2r1	1.573835774	3.38585E-08
Acp1	1.557569955	0.000261235
Gbp7	1.555388084	7.57036E-05
Tmprss11d	1.554846328	0.002565131
Rhoc	1.549877124	4.9658E-08
Ccdc88b	1.546309694	2.7261E-05
Fgr	1.543307444	0.002954787
Krt1	1.540248096	0.000161752
Hsd11b1	1.539121421	0.003728367
Rltpr	1.536677471	0.001873894
Tnfaip2	1.534797859	6.41706E-22
Ppp2r2c	1.531602156	0.001809933
Asb2	1.525632733	9.73362E-07
Ets1	1.524817188	2.04355E-13
Ccr1	1.514548667	0.001077273
P2ry10	1.51091329	0.002136684
Psmb9	1.507861764	5.86659E-07
Casp1	1.507006458	5.48495E-07
Atp6v1g2	1.502597153	3.3679E-06
Slco2b1	1.490041713	0.003241821
Oas1e	1.489985095	0.002856819
Gbp2b	1.485426612	0.003522974
Lix1l	1.484545872	6.3643E-08
Vcam1	1.481892988	0.000570118
Itgb7	1.477629277	0.000424397
Krt16	1.473964756	4.92006E-11
Psmb8	1.468655102	4.8278E-13
Usp35	1.466275909	2.43113E-05
Lppr2	1.463648215	7.46973E-18
Gm12942	1.463444105	6.47991E-08
Tmprss11b	1.459772285	0.001052143
Fcgr2b	1.459207252	0.000407716
Hsp90ab1	1.458004795	3.07521E-09
Akt3	1.451704949	0.000226061
Rinl	1.450509541	0.000528965
Ptger1	1.448562437	7.0429E-06
Lrrc32	1.448338914	3.57313E-06
Il1f6	1.447659593	3.27643E-10
A630023A22Rik	1.445492727	2.58015E-05
Adamts5	1.445301362	2.32845E-12
Parp14	1.4446802	2.12056E-10

4930524J08Rik	1.444065121	0.000905329
Fst	1.442738865	2.5538E-14
Krt12	1.441955562	0.005059335
Kcnip2	1.435748087	0.000600696
Tnfrsf23	1.431273359	2.44954E-10
Tas1r3	1.424785092	0.008886589
Notch4	1.421053645	0.000154891
Rp1l1	1.416874084	0.001606712
Elovl6	1.404519588	0.000901933
Ano7	1.395070174	4.01417E-06
BC100530	1.38835095	1.51921E-06
Far2	1.383858746	0.002195101
B2m	1.379895788	9.01899E-16
Slc7a3	1.379284788	0.005276774
Coro1a	1.378541738	4.59076E-06
1190005I06Rik	1.372988758	0.006396701
Enho	1.371719648	0.000477978
Defb6	1.371479895	3.58449E-07
Stab1	1.371439591	1.55919E-11
Zmat1	1.370486036	0.002338956
Dok3	1.366888127	0.000102213
Sprr2i	1.361525327	1.89933E-11
Klf2	1.36067873	0.000463746
Ptges	1.360132801	9.31974E-21
Hist2h3c2	1.35990535	0.000698934
Vim	1.353953652	4.24932E-14
Mgarp	1.352088069	2.51841E-06
Dlg4	1.3517709	0.001154768
Irgm2	1.342003782	7.74323E-05
Tdrd5	1.332225688	4.05864E-05
Fmnl1	1.32454261	7.65839E-05
Cidec	1.323611973	0.002388529
Gsdmd	1.318862445	0.000324693
Tmigd1	1.31691345	0.000196605
Lce1k	1.314200611	3.06696E-06
Agap2	1.306816594	1.94059E-09
Eda2r	1.304064289	1.58951E-10
Serpinb3a	1.290171397	5.71963E-09
Tmem240	1.288276346	0.006223369
Tbkbp1	1.286445136	6.95766E-05
Ctss	1.281983114	2.32335E-05
Kremen2	1.279217838	8.88012E-10
H2-M2	1.274909293	0.000193521
Serpinb1a	1.274715146	3.19516E-10

Zmynd15	1.272161815	0.000172857
Plod1	1.266502641	3.19516E-10
Fgfbp3	1.261790006	1.8243E-10
Cdhr1	1.261524428	0.001208473
C1rl	1.253907743	1.23164E-05
Rnf224	1.236063447	8.93336E-05
Rbp1	1.235442685	1.45781E-16
Kcnab2	1.232263077	0.001323203
Isg15	1.229937075	0.004799382
Rasl10a	1.213770978	6.42124E-05
Gm38119	1.211897505	0.00045725
Hap1	1.211340561	2.70921E-10
Lag3	1.209502858	0.000265427
Fam174b	1.209458227	0.001706874
4921536K21Rik	1.203229802	1.2284E-05
Oat	1.202028834	1.7847E-09
Lsp1	1.199125032	5.43558E-05
Pkdcc	1.196854035	0.000153731
Lrrc29	1.195152632	9.14962E-05
Agbl3	1.193393243	1.14119E-09
Col8a1	1.190208581	7.18382E-08
Icam5	1.188538385	6.76581E-07
Ly75	1.184912412	2.30916E-05
Tmem176a	1.181593968	6.8321E-10
Fas	1.177586048	0.001065651
Cyba	1.175404835	0.000487845
Tmem151a	1.174989274	9.02369E-07
Gjd3	1.174814453	0.002533001
Tnfsf18	1.173972425	0.002649254
Lat	1.169941928	0.006626504
Itgax	1.162489042	0.000340789
Dnhd1	1.154358672	0.000143204
Irf1	1.152309193	1.33336E-06
Rbp2	1.152174581	2.29358E-12
Wscd2	1.152106466	0.000601576
Tubal3	1.152102527	0.007562943
H2-Q4	1.148702009	4.43852E-05
Krt222	1.147184889	0.002381843
Anxa3	1.14686161	3.09785E-06
Tmem80	1.144960106	1.67381E-10
Lce6a	1.142422658	5.39448E-09
Kif26b	1.140830931	5.25865E-05
Selplg	1.139932891	3.85628E-05
Cd53	1.136208449	0.002822472

H2-T22	1.132000219	6.15817E-09
Spn	1.1251528	0.000638154
Lgals9	1.12183177	6.86959E-09
Tgfbr3l	1.120942178	0.00017857
Noxo1	1.118016648	2.22977E-06
Tle6	1.115395284	0.000448329
Lcp1	1.114584033	6.20328E-05
Tnfrsf25	1.114468972	0.000434425
Csf1	1.113633752	0.000200065
Itgae	1.109711816	0.003668098
Wfdc12	1.109679881	0.000367873
Elk3	1.103979318	2.84755E-06
Ybey	1.099768919	4.20173E-10
Nckap1l	1.09836085	0.000861462
Ggact	1.095909674	0.000226443
Serpinb12	1.095479028	3.29726E-06
Maneal	1.094458253	0.00398627
Hmha1	1.092803539	0.000263141
Pbx3	1.088727098	2.89623E-08
Cxcl16	1.083921222	7.89148E-10
Clec11a	1.078521113	1.01325E-05
Gm5689	1.077018704	4.8278E-13
Apobr	1.076959809	4.87173E-05
9030617O03Rik	1.076862882	0.001796449
Casq2	1.070288215	0.000536692
Zfp872	1.067888917	0.009962039
Tmem173	1.0677548	0.004052918
Kng2	1.066030109	0.000594842
Atf3	1.065355351	0.009821672
Pctp	1.064584067	1.11183E-09
Morn2	1.064103185	8.44486E-05
Tspan4	1.061875191	0.00031329
Tap2	1.061812691	5.34864E-10
Cep135	1.061449275	0.000408513
Flywch2	1.058722018	6.52811E-05
Aoc2	1.058253602	9.75131E-08
Fam162a	1.049821318	1.05134E-12
Ina	1.047481216	0.004000379
Gpm6b	1.046979905	0.005218922
3110062M04Rik	1.046039527	2.27416E-07
Mlkl	1.045480417	4.57792E-05
Upk1a	1.04403007	0.003825764
H2-Eb1	1.042248308	8.26218E-07
Itpka	1.040967333	0.004343132

Pglyrp3	1.040281782	0.000108119
Jak3	1.039237981	0.000487845
Sh2d5	1.036310468	0.002288553
Rbp7	1.031347501	1.23595E-07
Il1f5	1.031253951	1.08214E-07
Ldhb	1.031211386	1.21378E-09
Icam1	1.030354606	2.55228E-07
Bfsp1	1.030188656	3.40426E-06
C1qtnf6	1.029514441	0.004174722
Cyp3a13	1.028162535	4.34199E-07
Serpinb9	1.027089861	0.008812934
Arhgap30	1.025207634	9.08558E-06
Ppp1r14a	1.02351259	0.005156381
Zbtb48	1.022350347	1.11701E-10
Neurl1b	1.0194539	1.80078E-06
Col5a3	1.017807047	0.008812934
Flg	1.017633188	0.00035916
Acot5	1.017221714	1.35944E-05
Azin2	1.017003666	1.13486E-09
Tdrp	1.015613162	0.000644766
Acoxl	1.014305397	1.5101E-07
Tcaf2	1.012324303	3.09135E-07
Nsun5	1.010925087	2.2682E-12
Angptl4	1.010625871	0.000331721
Apoc1	1.007769351	6.86959E-09
Il33	1.004278997	0.000204035
Fhl3	1.003737961	1.21185E-05
Ccl22	1.001835942	4.66887E-06
Iqgap2	-1.004060618	0.005897679
Lap3	-1.005748064	8.85028E-08
Parp1	-1.007267422	2.09971E-11
Rnaset2a	-1.010531743	0.000507785
Vtcn1	-1.010764613	0.003723577
Gmpr	-1.011791608	0.009497407
Foxn1	-1.012345637	5.77868E-08
Sp6	-1.013668816	5.39448E-09
Dmpk	-1.014517811	5.69197E-08
Isoc2a	-1.017781609	3.88153E-06
Fstl1	-1.017867526	1.2988E-07
Rgl1	-1.02181208	3.62964E-05
Lyrm9	-1.021987568	8.73857E-06
Zdhhc15	-1.022326374	0.000157543
Mroh1	-1.024312927	5.59065E-10
Zfp786	-1.024927449	0.006934553

Ache	-1.026742114	9.76463E-06
Mical1	-1.027484337	3.48986E-11
Morn4	-1.027702553	0.001117848
Prickle1	-1.030264731	6.29E-07
Whrn	-1.032762693	2.07863E-06
Ngfr	-1.034502338	0.000751925
Tbc1d16	-1.037722838	9.50023E-08
Slc16a5	-1.038600973	0.00013107
Paqr8	-1.040364822	0.003202655
Tmem117	-1.041850602	1.90635E-05
Adamts9	-1.042237035	0.001077273
Zdhhc12	-1.042948063	0.001002224
Tspan13	-1.043015892	0.008573087
Dlx3	-1.047392892	2.13605E-06
Slc9a3r2	-1.047738199	0.008834333
Gm973	-1.050402199	4.29689E-05
Bmper	-1.051225039	0.002659409
Prkcq	-1.054019871	0.000374943
Skint10	-1.056902972	7.90313E-09
Papln	-1.058177477	0.000167712
Dapk1	-1.059848968	3.43148E-07
Npas2	-1.061383182	0.000119311
5330417C22Rik	-1.065529443	0.005733133
Foxq1	-1.066666888	3.18318E-10
Car6	-1.06750232	0.000274452
Gna14	-1.068097494	1.63321E-05
E2f7	-1.069761038	0.000136897
Pitpnc1	-1.074713002	7.55963E-08
Lgals3bp	-1.084948558	0.000136897
Rab44	-1.086003205	0.001922212
Otop2	-1.093862057	0.002129197
Kcng4	-1.095442812	0.002399151
Ccdc171	-1.100997152	0.001685961
Tmem45a2	-1.102796862	7.54719E-06
Cecr2	-1.105080225	8.34106E-05
Sptb	-1.109889144	0.003104057
Ptpru	-1.110851465	1.21424E-05
Cadm4	-1.110906206	3.02598E-05
C130074G19Rik	-1.113017456	0.007584093
Slc43a1	-1.113809261	1.01274E-06
Fn1	-1.115696191	7.65871E-06
Tet1	-1.11677107	0.004785037
Sema7a	-1.120747673	1.57182E-07
Kcnn1	-1.125586145	0.001470661

Rbms3	-1.137925579	0.000156467
Cntfr	-1.141216183	0.000144901
Cdc42ep2	-1.141281203	0.002659263
Cpxm1	-1.141510509	0.000167937
Slc6a4	-1.142958641	4.37242E-12
Grik5	-1.145901676	0.000145842
Cyp2f2	-1.146137445	0.004119352
Rnf128	-1.147628494	0.000237162
Man1c1	-1.150844194	7.74898E-05
Bmp4	-1.156001429	7.03476E-05
Tnfrsf22	-1.157687569	0.000752728
Selenbp1	-1.159781968	3.16434E-12
Dlx1	-1.159928056	2.7261E-05
Tnik	-1.165670792	5.28645E-05
Tmod2	-1.165974309	0.007701554
Srl	-1.166566047	2.74923E-07
Hoxc13	-1.167893215	4.45346E-09
Grem1	-1.168917857	0.002198622
Rasl11b	-1.171176609	0.001298316
Ggt1	-1.171327471	0.005978384
Rhpn2	-1.175231992	4.83181E-05
Nrcam	-1.17631259	0.000269588
Sox6	-1.179194372	7.08337E-08
Pls1	-1.180880281	0.003745835
Phactr1	-1.181982229	0.000639776
Rerg	-1.183179735	3.99699E-07
Frem2	-1.18810264	0.000273765
Adap1	-1.189322063	2.01986E-05
Ctps	-1.197481746	2.69883E-15
Susd4	-1.20394234	3.88571E-10
Slc30a2	-1.204099337	0.007381624
Serpinb7	-1.204875062	1.60632E-15
Acot12	-1.207073048	0.003269479
Fam20a	-1.211117792	7.80325E-08
Lmod2	-1.215371078	0.001376363
Osbpl10	-1.216519316	7.01462E-07
Krtap3-1	-1.217224229	0.000503954
Dcp1b	-1.21826797	2.01729E-11
Fxyd4	-1.219256014	0.000597777
Htr1d	-1.21955686	5.48495E-07
Fhod3	-1.221017983	3.63604E-06
Vcan	-1.222285989	9.78274E-06
Rnf180	-1.227192731	0.000566501
Ikzf4	-1.227848918	1.2318E-07

Efemp1	-1.228579612	1.67381E-10
Zfp937	-1.228896517	0.003510394
Tbc1d30	-1.233564609	3.3989E-10
Eid2	-1.239503504	0.003967921
Ahnak2	-1.246124702	1.78972E-11
Prom1	-1.249579058	0.00690114
A530016L24Rik	-1.251391758	0.003546523
Cpm	-1.251830564	4.68948E-05
Col14a1	-1.25435714	6.46595E-06
Cfap70	-1.256422368	0.008473109
Arid3a	-1.257186427	1.72017E-11
Zfp612	-1.257439267	0.000155141
Dclk2	-1.267904706	1.27706E-05
P2ry2	-1.268512874	7.36174E-08
Ccl28	-1.273220812	8.87025E-06
Dennd2a	-1.275290717	0.007416388
Serpinb6d	-1.276831852	1.1035E-05
Lgals7	-1.286379781	5.53721E-05
Il20ra	-1.288294013	0.004822713
Trim15	-1.28862445	0.001979653
Gldc	-1.289697937	0.000151242
D6Ertd527e	-1.297515511	0.002793491
Capn12	-1.297978716	3.78151E-12
Tspan7	-1.298739905	1.65753E-14
Cdkn1c	-1.306040553	0.004962898
Eln	-1.308012012	0.00056953
Zfp608	-1.316022735	2.74671E-07
Cyp2b23	-1.316932038	6.53537E-06
Ica1l	-1.320641656	0.000970042
Aldh3b3	-1.325540724	7.10532E-16
Clec2e	-1.329606349	0.000119398
Ptger3	-1.331859146	0.000145842
Smad9	-1.333999258	0.000476068
F3	-1.335917542	2.28164E-18
Acvr2b	-1.34021805	0.009751475
Lonrf3	-1.340231513	0.000200543
Zfhx2	-1.344243102	1.48525E-07
Prss53	-1.345172883	1.47884E-06
Ephb1	-1.345770007	0.0006656
Pdia5	-1.351434904	0.000636776
Rpp25	-1.353788661	0.000761341
Fmo1	-1.360063269	5.99145E-05
Chd5	-1.360843632	0.007100269
Svip	-1.368117026	2.64015E-08

Cygb	-1.369908462	8.55287E-05
Mgat5b	-1.374495781	3.95173E-06
Lrat	-1.376488908	0.000979439
Cilp	-1.37876731	0.005357691
Mfsd4	-1.388034902	3.70109E-10
Sod3	-1.3901562	0.005111228
Pde1c	-1.398472994	0.000148662
Sulf1	-1.407431916	0.003141655
Lmtk3	-1.411268838	0.000244474
D730001G18Rik	-1.411619181	0.000818573
Psors1c2	-1.412281331	9.13045E-10
Ccdc69	-1.413242859	0.003910513
Gm13177	-1.416402175	7.27973E-11
Entpd3	-1.42432949	1.05853E-06
Tacr3	-1.430759684	0.000236258
Palm3	-1.432162325	2.59466E-06
Igfbp5	-1.440220178	9.84189E-06
Foxc2	-1.443502975	1.1035E-05
Hmgn2	-1.446368327	0.00640313
Tnfrsf13c	-1.45200694	4.83181E-05
Cd19	-1.458543859	0.002601025
Rasd2	-1.460183252	0.000152995
Cybrd1	-1.46350546	3.00325E-08
Nup210	-1.473790262	1.4021E-09
Dlx4	-1.475420392	3.47776E-09
Gm11569	-1.486852988	0.005865179
Cacna1d	-1.486882236	7.98147E-05
Ccdc109b	-1.493573758	3.0162E-06
Nmnat2	-1.495509865	0.000483754
Slc4a9	-1.510390596	5.62747E-08
Tll1	-1.513240696	0.000752587
Hpgd	-1.517110808	6.62252E-23
Trpm6	-1.518664171	0.000730397
Lrrc31	-1.519827096	0.000296831
Cysltr1	-1.520042339	0.001324746
Krt32	-1.521351633	0.002693656
Nkd1	-1.521447317	7.48229E-09
Lppr3	-1.524055367	1.22967E-09
Igfbp3	-1.524854196	5.62097E-05
Rab37	-1.527502746	0.001321488
Kcne1	-1.528114151	0.008993478
Sstr2	-1.530415749	0.002692875
Mex3a	-1.533068876	7.99085E-15
Plce1	-1.535365014	0.002630921

Cdh4	-1.538582835	1.4661E-05
Pde9a	-1.538920623	0.000647817
Gja1	-1.54177872	6.96801E-10
Coro6	-1.550953097	0.00438051
Fras1	-1.55485205	8.11599E-05
Slc5a5	-1.5570641	0.000290651
Selenbp2	-1.557330487	9.82796E-20
Gpr176	-1.557538995	0.000182769
Gatm	-1.562184606	2.49303E-06
Kcng2	-1.567500991	0.001566227
Ifi205	-1.568025485	0.001438505
Mest	-1.57108776	1.17898E-05
Cldn8	-1.571891363	4.74167E-12
Tspear	-1.579852227	0.000309069
Mtcl1	-1.586258209	6.28913E-11
Ebf4	-1.58816803	0.001139128
Krtap3-3	-1.588324369	0.000148329
Bambi	-1.590090658	1.85066E-10
Nim1k	-1.598537043	1.11383E-05
Pvrl3	-1.600752699	0.000133938
Elf5	-1.60187165	5.01557E-09
Cystm1	-1.602810345	2.0344E-09
Adamts14	-1.604745681	2.5401E-15
Srms	-1.613312405	2.1157E-07
Ldoc1l	-1.620784883	6.00469E-06
Snhg11	-1.622432128	3.40226E-08
Ccr4	-1.62716433	7.57885E-05
Hecw2	-1.631533382	7.71759E-05
Krt73	-1.632066943	0.00250614
Hspa12a	-1.633361509	3.26361E-19
Spock2	-1.637455199	6.9067E-28
Fam228b	-1.637735442	0.000741722
Xpnpep2	-1.637800707	6.37555E-06
Slc18a1	-1.637985633	0.000348099
Smc1b	-1.642184402	0.004502668
Gpr156	-1.648313735	1.70531E-05
Msx1	-1.648907036	5.07508E-05
Krt28	-1.651752676	0.001385896
Tmem28	-1.652916397	7.54241E-07
Golga7b	-1.658301288	8.77596E-06
Slc38a3	-1.658751366	7.08425E-07
Ceacam1	-1.661351594	0.003847129
Muc3a	-1.666817043	5.75245E-05
Rassf2	-1.680382382	1.90635E-05

Ccdc149	-1.684245748	2.19212E-05
Gnmt	-1.685263422	0.000455343
Igf2	-1.689140615	0.000142777
Slc4a1	-1.689351182	0.00079114
Tchh	-1.698076959	0.000969344
Bean1	-1.698792328	0.000587802
Gabrp	-1.706250344	0.000424397
Fgd5	-1.707700753	0.005471903
Ccdc158	-1.713530059	0.000671563
Cxxc4	-1.718619132	0.000132519
Ugt2b1	-1.72531576	0.005944941
Fam49a	-1.73516181	7.9917E-07
Krt71	-1.740036414	0.002466243
Xkr6	-1.743145304	1.45002E-09
Dclk3	-1.74438736	0.000144549
Zfp941	-1.744776486	0.000707279
Fndc4	-1.747045457	4.50096E-07
Cldn10	-1.751819926	6.27798E-06
Ablim2	-1.75743324	5.78836E-05
Steap1	-1.760316056	7.55609E-06
Slc39a8	-1.772190206	0.000357038
Gpm6a	-1.783744612	5.32781E-14
Mpo	-1.786283145	0.002815094
Kcp	-1.791798205	0.00261773
Pm20d1	-1.792782934	4.29066E-32
Upp1	-1.794079184	0.000411853
Mlf1	-1.798030263	3.22543E-14
Eml1	-1.799087089	7.228E-16
Cryba4	-1.799203605	0.001570645
Gm7735	-1.803622532	7.60444E-06
Myb	-1.803923925	1.81192E-07
Chac1	-1.807587136	7.40378E-16
Heyl	-1.811321626	0.002983543
Gja3	-1.82001441	6.45954E-08
Fap	-1.826744309	0.000466863
Fam124b	-1.82786417	4.3521E-07
Oprd1	-1.829627351	0.000843694
En1	-1.831600624	0.000513164
Scn4b	-1.832181743	2.1662E-05
Krtap27-1	-1.837078961	5.62097E-05
Bend5	-1.837536604	7.39518E-10
Krtap6-2	-1.847137771	1.72425E-08
Nxf7	-1.863366871	0.000181181
Olfml2b	-1.870643331	7.29165E-05

Mal	-1.870969017	8.00963E-06
Gm11554	-1.873472031	9.66221E-05
Reep1	-1.874819019	1.96046E-09
Gng4	-1.875233941	1.23186E-07
Eci3	-1.878727648	0.004699534
Ccnjl	-1.884392048	0.002805295
Scara5	-1.889100139	0.002568308
Gpr50	-1.890283864	2.20156E-05
Akap12	-1.890442472	7.39587E-07
Prrt1	-1.892076949	9.07556E-06
Nsg1	-1.892202444	1.72017E-11
Lef1	-1.893027933	4.38852E-09
Slc35f1	-1.893135932	5.43272E-07
Ly6g6d	-1.899686778	0.000128716
Msx2	-1.903144918	6.28913E-11
Myef2	-1.913418783	8.26722E-11
Krtap20-2	-1.914210347	6.96535E-12
Gm11564	-1.915940802	0.000781316
Mettl7a3	-1.922357452	1.97263E-06
Gfra3	-1.922536107	5.4051E-07
Krt27	-1.932209761	0.001183934
Nrxn2	-1.936190215	1.97531E-07
Krtap3-2	-1.943491018	3.80019E-10
Gfra2	-1.945310721	0.000208649
Dysf	-1.952866494	2.46299E-08
St8sia6	-1.958887778	1.42421E-05
Dnajc6	-1.960123395	4.65883E-09
Procr	-1.967369513	1.01274E-06
B4galnt4	-1.974211793	7.36536E-11
Adrb1	-1.978425781	2.18331E-07
Rgs6	-1.982074848	0.000752728
2310079G19Rik	-1.993246612	0.001544723
Gm438	-2.002058479	1.68475E-22
Krt39	-2.005277415	2.47386E-06
Atp8b5	-2.016909843	0.001124375
Ccdc155	-2.022692603	3.99699E-07
S100a3	-2.030793533	0.000107123
Fbp1	-2.03307297	0.000375002
Cldn14	-2.034918745	0.000407135
Gm9833	-2.035634706	2.11812E-06
Galnt9	-2.044729375	5.50884E-06
Gpc3	-2.045372652	3.15545E-18
Serpina1e	-2.062081639	0.000739572
Dusp2	-2.063991397	2.79614E-07

Stox1	-2.07441413	7.50024E-05
Il1f10	-2.081587466	3.55642E-08
Gprc5a	-2.082290598	5.18776E-05
Bhlha9	-2.090391028	0.000688413
Efhd1	-2.095352116	9.61603E-11
Zfp618	-2.099872091	2.45477E-39
Ctse	-2.102691496	9.73026E-05
Fam169a	-2.118579894	0.000682774
Nkd2	-2.128456488	3.26968E-07
Prdm8	-2.131090129	0.001838085
Pcp4	-2.134890436	8.30587E-07
Myo5c	-2.143510814	6.1443E-09
Slc9a2	-2.149807462	4.57792E-05
Tigd4	-2.151579783	6.5039E-08
Gm10228	-2.172046743	1.0121E-09
Krt82	-2.182144456	0.00363494
Rnf182	-2.193947642	2.98102E-06
Dsg4	-2.196393593	0.000156479
Krtap6-1	-2.219588854	5.02769E-07
Skint11	-2.227419012	2.04669E-10
Lrrc15	-2.238065612	1.92437E-10
Krtap16-1	-2.238163589	0.001130784
Krtap9-5	-2.239650443	3.16972E-06
Krtap24-1	-2.239869449	0.002094061
Padi1	-2.24143625	2.3848E-06
Prr9	-2.248166713	2.04709E-11
Npy1r	-2.262725708	1.98863E-06
Krt74	-2.275954929	5.55206E-07
Padi3	-2.280068506	0.000244363
Krtap21-1	-2.283547921	3.51027E-10
Csdc2	-2.295905398	3.60766E-09
S100a7a	-2.296041996	1.39135E-08
Rgs16	-2.296596239	2.1383E-05
Krt40	-2.321606551	0.000600181
Krtap17-1	-2.321898671	1.27436E-06
Pkdrej	-2.323794459	0.000107979
Rtkn2	-2.346184154	1.2987E-08
Sptssb	-2.35403826	7.1994E-07
Krtap13-1	-2.369384887	2.46055E-07
Syt7	-2.382621131	6.68065E-09
Tesc	-2.384053329	2.87323E-15
Il22ra2	-2.384254895	4.82479E-09
Capn8	-2.384773319	2.89226E-07
Bmp8a	-2.386111335	9.75131E-08

Scgb1a1	-2.389153574	2.16994E-18
Krtap6-5	-2.390259491	1.40149E-09
Bex1	-2.39735538	1.04619E-05
Chrna4	-2.411209551	0.000834734
Crnn	-2.415867222	2.97211E-08
Zpbp	-2.436588443	1.90635E-05
Krt25	-2.439247604	0.000820776
Vsig8	-2.445733594	0.000370171
Krt26	-2.454577579	0.000414244
1110025L11Rik	-2.470151097	1.3995E-07
Itga11	-2.477444422	1.42646E-05
Grm4	-2.481652115	2.10802E-10
Gm3250	-2.488278754	1.11416E-08
Krtap22-2	-2.489617149	2.1348E-10
Krt72	-2.489701735	0.000148852
Krtap26-1	-2.492125566	3.34894E-06
Krtap10-4	-2.502256535	0.000246438
Lyg2	-2.50701389	0.000933096
Foxl1	-2.514146811	0.001545073
Tmprss11c	-2.519929246	0.00043496
Klk15	-2.52368422	6.87658E-08
Sez6	-2.531976297	0.002767117
Gm3233	-2.534882924	9.14251E-06
Crym	-2.552400659	4.79172E-06
Gm7138	-2.555380012	1.85066E-10
Krt31	-2.575171731	6.37958E-05
Krtap4-16	-2.581645002	2.25559E-05
Gm3238	-2.587727845	6.43614E-05
Actbl2	-2.594303484	2.34394E-05
Slco4c1	-2.597861113	4.97553E-05
Krt34	-2.599388566	9.78274E-06
Kcnk16	-2.636296702	8.8273E-05
Gm11562	-2.641350221	2.84632E-09
Pla2g4c	-2.646173198	9.03207E-15
Fam26d	-2.647676767	0.000209221
5430421N21Rik	-2.648366982	6.43301E-06
Krt83	-2.650453549	1.43813E-06
Gm10272	-2.654932496	7.60444E-06
Krt86	-2.671458891	1.06086E-05
Fabp4	-2.693339413	1.49004E-12
Slc13a2	-2.693614521	0.006699166
Gm10229	-2.695501376	1.38824E-09
Csmd2	-2.704266096	0.000130488
Grik4	-2.704428864	1.36979E-19

Gm10142	-2.707049729	1.79872E-06
Krtap11-1	-2.710909734	1.72766E-05
Rgs7bp	-2.723712428	1.97531E-07
Car8	-2.727010765	1.42708E-05
Gm11938	-2.745562606	6.11973E-08
Krtap4-8	-2.747906331	1.5101E-07
Krtap4-9	-2.748577738	4.59821E-07
Krtap19-5	-2.75142545	1.51539E-08
Gm11937	-2.754419141	1.2183E-07
Cpxm2	-2.764628007	4.65735E-50
Krtap12-1	-2.77128549	1.1035E-05
Krt81	-2.774425057	4.12154E-06
Gm266	-2.776176381	2.54558E-10
Dio3	-2.77941411	1.34521E-11
Adamts19	-2.784471759	2.63997E-05
Pax7	-2.788219434	4.83181E-05
Krtap2-4	-2.788916728	5.77165E-08
Gm19402	-2.791499326	6.8247E-06
Gm11939	-2.798583318	9.91565E-19
Tagln3	-2.799229629	4.87383E-08
Gm9507	-2.80438723	8.87864E-05
Krt33b	-2.809277596	8.9707E-06
Gm10024	-2.825292875	7.08568E-05
Gm11595	-2.854793187	6.63124E-08
Gm11596	-2.857677717	4.33668E-08
Gm19668	-2.858712033	1.50898E-06
Gprc5d	-2.871884753	7.1994E-07
Krtap4-2	-2.876686498	3.17171E-08
Krtap1-3	-2.879373593	5.7069E-07
Syt17	-2.890451029	6.51568E-10
Krtap29-1	-2.895859207	2.22911E-09
Skint6	-2.900927483	2.24804E-23
Tchhl1	-2.907731533	1.50725E-10
Gm11568	-2.908526281	1.29009E-06
Krtap4-7	-2.91398894	1.78054E-07
Gm7137	-2.916935428	1.60793E-11
Cacna1i	-2.924081905	1.49045E-05
Mcpt1	-2.929058195	2.68907E-06
Gm11563	-2.950776363	7.54361E-08
Krtap1-4	-2.950894008	3.75498E-07
Slc26a3	-2.95610856	1.30539E-05
Slco5a1	-2.961304037	6.33496E-08
Tm4sf4	-2.973220132	3.39684E-07
Myom2	-2.976942234	4.24932E-14

Krt33a	-2.988912655	1.48924E-05
Prr5l	-3.00190194	1.40801E-12
Krtap9-3	-3.002199979	1.92628E-07
Gm11555	-3.038827069	1.0316E-08
Krtap4-1	-3.048323868	6.66748E-08
Krtap19-4	-3.070748245	4.21077E-07
Ifitm6	-3.076503284	1.85044E-05
Krtap4-13	-3.082121515	4.20477E-11
Gm10100	-3.112213951	3.62528E-07
Krtap6-3	-3.139561986	1.17596E-15
Cdh6	-3.158513135	6.65201E-10
Krtap4-6	-3.171133216	5.10367E-09
Gm11559	-3.1897993	7.31455E-07
Gm9789	-3.266386675	9.38716E-15
Gm11567	-3.294143605	9.75131E-08
Kcnn3	-3.29895543	0.000196629
Krtap9-1	-3.323377576	1.57182E-07
Krtap8-1	-3.416045085	1.8243E-10
Slc6a13	-3.417379874	1.14647E-09
Krtap19-3	-3.430161668	5.45638E-10
Krtap14	-3.440406152	9.09171E-08
Krtap15	-3.478945133	5.54133E-07
Krtap1-5	-3.491914134	8.71638E-10
Crisp1	-3.510979271	0.00010015
Krtap19-9b	-3.523189558	3.4226E-09
Apba2	-3.535020946	7.33937E-14
0610040J01Rik	-3.539111308	3.34626E-21
Krtap31-1	-3.539655678	7.10884E-14
Krtap19-9a	-3.580508701	8.35191E-12
Krtap7-1	-3.589561545	1.79772E-12
Gadl1	-3.615695474	6.58278E-18
Ccdc80	-3.639550869	4.37034E-26
Krtap19-2	-3.664810219	5.74446E-07
Gm6358	-3.666610846	3.54636E-15
1110057P08Rik	-3.681039574	9.25208E-41
Gm11565	-3.681376756	1.63051E-21
Krtap16-3	-3.727720341	1.11493E-10
Gm10153	-3.757762644	2.20536E-17
Krtap5-5	-3.769537723	3.99624E-08
Krtap19-1	-3.844610307	4.38272E-09
Krtap5-3	-3.847258335	7.91006E-10
Krtap5-2	-3.856372316	3.23441E-10
Krtap28-13	-3.963397758	1.5323E-08
Gm4553	-3.970478793	1.07964E-29

Stk33	-3.987568342	1.45121E-08
Gm4559	-3.992923633	3.4901E-21
Gm2431	-4.058621123	1.07964E-29
Krtap31-2	-4.14950965	2.16359E-18
Krtap5-4	-4.160511689	6.96535E-12
Rasgrf2	-4.232670612	6.77847E-26
Ogn	-4.244275854	9.2366E-46
Krtap5-1	-4.296088346	9.67429E-31
Hhip	-4.364200841	1.88577E-31
Skint9	-6.745196022	7.72867E-52
Skint3	-7.298019329	4.29114E-75
Skint4	-7.504350272	1.72776E-81

SUPPLEMENTARY TABLE S5: Downregulated DEGs (SKOvsCTR) are enriched for *Krt* and *Krtap* genes.

Gene name	SKOvsCTR : logFC	SKOvsCTR : FDR
Krtap5-1	-4.296088346	9.67429E-31
Krtap5-4	-4.160511689	6.96535E-12
Krtap31-2	-4.14950965	2.16359E-18
Krtap28-13	-3.963397758	1.5323E-08
Krtap5-2	-3.856372316	3.23441E-10
Krtap5-3	-3.847258335	7.91006E-10
Krtap19-1	-3.844610307	4.38272E-09
Krtap5-5	-3.769537723	3.99624E-08
Krtap16-3	-3.727720341	1.11493E-10
Krtap19-2	-3.664810219	5.74446E-07
Krtap7-1	-3.589561545	1.79772E-12
Krtap19-9a	-3.580508701	8.35191E-12
Krtap31-1	-3.539655678	7.10884E-14
Krtap19-9b	-3.523189558	3.4226E-09
Krtap1-5	-3.491914134	8.71638E-10
Krtap15	-3.478945133	5.54133E-07
Krtap14	-3.440406152	9.09171E-08
Krtap19-3	-3.430161668	5.45638E-10
Krtap8-1	-3.416045085	1.8243E-10
Krtap9-1	-3.323377576	1.57182E-07
Krtap4-6	-3.171133216	5.10367E-09
Krtap6-3	-3.139561986	1.17596E-15
Krtap4-13	-3.082121515	4.20477E-11
Krtap19-4	-3.070748245	4.21077E-07
Krtap4-1	-3.048323868	6.66748E-08
Krtap9-3	-3.002199979	1.92628E-07
Krt33a	-2.988912655	1.48924E-05
Krtap1-4	-2.950894008	3.75498E-07
Krtap4-7	-2.91398894	1.78054E-07
Krtap29-1	-2.895859207	2.22911E-09
Krtap1-3	-2.879373593	5.7069E-07
Krtap4-2	-2.876686498	3.17171E-08
Krt33b	-2.809277596	8.9707E-06
Krtap2-4	-2.788916728	5.77165E-08
Krt81	-2.774425057	4.12154E-06
Krtap12-1	-2.77128549	1.1035E-05
Krtap19-5	-2.75142545	1.51539E-08
Krtap4-9	-2.748577738	4.59821E-07
Krtap4-8	-2.747906331	1.5101E-07
Krtap11-1	-2.710909734	1.72766E-05
Krt86	-2.671458891	1.06086E-05
Krt83	-2.650453549	1.43813E-06

Krt34	-2.599388566	9.78274E-06
Krtap4-16	-2.581645002	2.25559E-05
Krt31	-2.575171731	6.37958E-05
Krtap10-4	-2.502256535	0.000246438
Krtap26-1	-2.492125566	3.34894E-06
Krt72	-2.489701735	0.000148852
Krtap22-2	-2.489617149	2.1348E-10
Krt26	-2.454577579	0.000414244
Krt25	-2.439247604	0.000820776
Krtap6-5	-2.390259491	1.40149E-09
Krtap13-1	-2.369384887	2.46055E-07
Krtap17-1	-2.321898671	1.27436E-06
Krt40	-2.321606551	0.000600181
Krtap21-1	-2.283547921	3.51027E-10
Krt74	-2.275954929	5.55206E-07
Krtap24-1	-2.239869449	0.002094061
Krtap9-5	-2.239650443	3.16972E-06
Krtap16-1	-2.238163589	0.001130784
Krtap6-1	-2.219588854	5.02769E-07
Krt82	-2.182144456	0.00363494
Krt39	-2.005277415	2.47386E-06
Krtap3-2	-1.943491018	3.80019E-10
Krt27	-1.932209761	0.001183934
Krtap20-2	-1.914210347	6.96535E-12
Krtap6-2	-1.847137771	1.72425E-08
Krtap27-1	-1.837078961	5.62097E-05
Krt71	-1.740036414	0.002466243
Krt28	-1.651752676	0.001385896
Krt73	-1.632066943	0.00250614
Krtap3-3	-1.588324369	0.000148329
Krt32	-1.521351633	0.002693656
Krtap3-1	-1.217224229	0.000503954

SUPPLEMENTARY TABLE S6: Overlap of upregulated DEGs (SKOvsCTR) and the GO_Immune_System_Process gene set.

Gene name	SKOvsCTR : logFC	SKOvsCTR : FDR
Ccl2	5.569476383	2.4143E-32
Ccl1	4.96704325	2.31247E-33
S100a9	4.622518139	1.43652E-10
Ccl20	4.228922878	4.66147E-23
S100a8	4.174235752	5.45686E-11
Pglyrp2	4.100906903	5.13833E-45
Blk	3.385207475	9.2625E-09
Cxcl10	3.2093752	1.16146E-08
Tnfsf4	3.157810331	8.93336E-05
Icos	3.025441396	0.000115095
Cxcl9	2.988683416	0.000689781
Il2rg	2.924128947	5.27519E-08
Ltb	2.917122347	7.03577E-06
Ccr2	2.906344841	2.25655E-08
Epb42	2.879079741	8.41099E-07
Gbp2	2.861369161	1.03382E-06
Cxcl1	2.837231096	7.51794E-07
Il18r1	2.821486218	1.32664E-17
Ccl7	2.818406405	0.000224406
Cd247	2.7702066	6.69687E-06
Igsf6	2.640476991	1.96569E-05
Cd3e	2.608574217	1.26872E-05
Ctsk	2.583007451	0.00012796
Il18rap	2.43188571	6.72608E-06
Tnf	2.364621827	2.13605E-06
Slc16a3	2.331840536	3.83735E-22
Pmaip1	2.270588654	7.92366E-09
Lax1	2.231451207	2.10887E-20
Mmp9	2.21669885	2.68206E-10
Lcn2	2.114326884	3.1714E-10
Slpi	2.062517659	5.56526E-12
Casp4	2.037305091	0.000272302
Artn	2.033294683	2.40136E-07
Mx1	1.989569898	9.55259E-05
Chga	1.940190275	3.60766E-09
Lif	1.870071066	4.10946E-07
Il7r	1.867356535	1.58689E-08
Dock2	1.719123784	0.000113138
Nlrc5	1.710007555	9.31974E-21
Fgr	1.543307444	0.002954787
Krt1	1.540248096	0.000161752
Rltpr	1.536677471	0.001873894

Ets1	1.524817188	2.04355E-13
Ccr1	1.514548667	0.001077273
Psmb9	1.507861764	5.86659E-07
Vcam1	1.481892988	0.000570118
Itgb7	1.477629277	0.000424397
Krt16	1.473964756	4.92006E-11
Psmb8	1.468655102	4.8278E-13
Fcgr2b	1.459207252	0.000407716
Hsp90ab1	1.458004795	3.07521E-09
Il1f6	1.447659593	3.27643E-10
Fst	1.442738865	2.5538E-14
Notch4	1.421053645	0.000154891
B2m	1.379895788	9.01899E-16
Coro1a	1.378541738	4.59076E-06
Klf2	1.36067873	0.000463746
Gsdmd	1.318862445	0.000324693
Tbkbp1	1.286445136	6.95766E-05
Ctss	1.281983114	2.32335E-05
C1rl	1.253907743	1.23164E-05
Kcnab2	1.232263077	0.001323203
Isg15	1.229937075	0.004799382
Ly75	1.184912412	2.30916E-05
Fas	1.177586048	0.001065651
Cyba	1.175404835	0.000487845
Tnfsf18	1.173972425	0.002649254
Lat	1.169941928	0.006626504
Itgax	1.162489042	0.000340789
Irf1	1.152309193	1.33336E-06
Anxa3	1.14686161	3.09785E-06
Selplg	1.139932891	3.85628E-05
Spn	1.1251528	0.000638154
Lgals9	1.12183177	6.86959E-09
Lcp1	1.114584033	6.20328E-05
Tnfrsf25	1.114468972	0.000434425
Csf1	1.113633752	0.000200065
Nckap1l	1.09836085	0.000861462
Serpinb12	1.095479028	3.29726E-06
Cxcl16	1.083921222	7.89148E-10
Tmem173	1.0677548	0.004052918
Tap2	1.061812691	5.34864E-10
H2-Eb1	1.042248308	8.26218E-07
Pglyrp3	1.040281782	0.000108119
Jak3	1.039237981	0.000487845
Il1f5	1.031253951	1.08214E-07

Icam1	1.030354606	2.55228E-07
Serpinb9	1.027089861	0.008812934
Il33	1.004278997	0.000204035
Ccl22	1.001835942	4.66887E-06