International Archives of Allergy and Immunology

Experimental Allergy – Research Article

Int Arch Allergy Immunol 2022;183:1040–1049
DOI: 10.1159/000525656

Received: April 27, 2022
Accepted: June 17, 2022
Published online: August 5, 2022

Skin Treatment with Detergent Induces Dermatitis with H1-Antihistamine-Refractory Itch and Upregulates IL-4 and Th17/Th22 Cytokine Gene Expression in C57BL/6 Mice

Yurie Masutani[a, b] Toshiro Takai[a] Seiji Kamijo[a] Toru Kimitsu[a, b] Tomoko Yoshimura[a, b] Saori Ichikawa[c] Saya Shimizu[a] Takasuke Ogawa[b] Keiko Takada[a, b] Mitsutoshi Tominaga[d] Hajime Suto[a] Kenji Takamori[d] Hideoki Ogawa[b] Ko Okumura[a] Shigaku Ikeda[a, b]

[a]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan; [b]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan; [c]Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University, Tokyo, Japan; [d]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender-Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan

Keywords
Murine model · Detergent-induced irritant contact dermatitis · H1-antihistamine-refractory dermatitis · IL-4 · Th17/Th22 cytokines

Abstract
Introduction: Repeated skin contact to detergents causes chronic irritant contact dermatitis (ICD) associated with itch sensation and eczema. However, the mechanisms of detergent-induced ICD are poorly understood. Here, we established a new murine model of detergent-induced ICD with H1-antihistamine-refractory itch. ***Methods:*** Ear skin of wild-type and mast cell-deficient mice on the C57BL/6 genetic background was treated with a detergent, sodium dodecyl/lauryl sulfate (SDS), daily for approximately 2 weeks with or without administration of an H1-antihistamine, fexofenadine. Skin inflammation, barrier dysfunction, and itching were analyzed. Quantitative PCR for earlobe gene expression and flow cytometry analysis for draining lymph node cells were conducted. ***Results:*** SDS treatment induced skin inflammation with ear swelling, increased transepidermal water loss, and hind-paw scratching behaviors in the wild-type and mast cell-deficient mice. The peak value of scratching bouts was retained for at least 48 h after the last SDS treatment. H1-antihistamine administration showed no or little reduction in the responses. SDS treatment upregulated gene expression for a Th2 cytokine IL-4 and Th17/Th22 cytokines, IL-17A, IL-17F, and IL-22, and increased cell numbers in draining lymph nodes of $CD4^+$ T, $CD8^+$ T, and γδT cells with enhanced expression of GATA3, RORγt, T-bet, or FOXP3 compared with untreated mice. ***Conclusions:*** The present study showed that SDS treatment of ear skin in C57BL/6 mice induces mast cell-independent skin inflammation with H1-antihistamine-refractory itch and suggested a possible Th cytokine- and/or lymphocyte-mediated regulation of the model. The model would be useful for elucidation of mechanisms for inflammation with H1-antihistamine-refractory itch in detergent-induced ICD.

Edited by: H.-U. Simon, Bern.

Karger@karger.com
www.karger.com/iaa

Correspondence to:
Toshiro Takai, t-takai@juntendo.ac.jp

Introduction

We use detergents daily for body washing, laundry, dishwashing, house cleaning, and so on. Exposures of skin to detergents can cause barrier disruption and inflammatory responses [1–5], leading to irritant contact dermatitis (ICD) associated with itch sensation and eczema [6, 7]. Another example of skin inflammatory diseases with barrier dysfunction is atopic dermatitis, in which patients suffer from chronic and recurring eczema, skin inflammation, and itch [8–11]. Allergens and irritants can be considered to penetrate through the barrier-disrupted skin, leading to sensitization to induce allergen-specific IgE production and a variety of Th subset development, such as Th2, Th22, and Th17 [12–16]. In murine models, skin pretreatment with a detergent facilitates epicutaneous allergen sensitization, leading to the onset of asthma and food allergy [17, 18].

Murine models using a model detergent, sodium dodecyl/lauryl sulfate (SDS), have been analyzed for elucidation of mechanisms of the detergent-inducible dermatitis [19–26]. While itch sensation was not reported [19–22] or not inducible [24] in most of these models, Inami et al. [25] demonstrated that 4-day treatment of shaved back skin with 10% SDS in ICR mice induced itch. SDS-treated mast cell-deficient WBBF1-*W/W*^{v} and their normal littermates showed equivalent numbers of scratching bouts. The itch sensation in ICR mice in the model can be suppressed by administration of an antagonist for the H1 histamine receptor. However, as far as we know, no SDS-inducible models of ICD with H1-antihistamine-refractory itch have been reported.

Animal models of skin inflammation with H1 antihistamine-refractory itch would be useful for elucidation of mechanisms for refractory subtypes in itch-associated skin diseases such as atopic dermatitis, psoriasis, contact dermatitis, and so on [27–29]. In the present study, we examined induction of itch-associated inflammation in C57BL/6 mice on earlobe skin treatment of with 10% SDS for approximately 2 weeks and demonstrated that this strain showed H1-antihistamine-refractory itch. In addition, we found upregulated gene expression of IL-4 and Th17/Th22 cytokines in the model.

Materials and Methods

Mice

Seven- to twelve-week-old C57BL/6J (Sankyo Lab Service Corporation, Ibaraki, Japan) and mast cell-deficient (*Kit*$^{W\text{-}sh/W\text{-}sh}$ [Wsh]) female mice with the C57BL/6J genetic background were maintained in a specific pathogen free animal facility at Juntendo University. All animal experiments were performed in accordance with guidelines of the Laboratory Animal Experimentation at Juntendo University School of Medicine.

SDS Treatment

Earlobe skin of mice was treated with SDS (Wako, Japan) every day. The SDS solution (10% SDS in pure water) was applied with a micropipette to both sides of the surface of the both ears and dorsal hairless area at the base of ear of lightly anesthetized mice (30 μL/ear, 60 μL/mouse).

Skin Inflammation and Barrier Dysfunction

Ear thickness of lightly anesthetized mice was measured using a dial thickness gage (G-1A, Ozaki, Tokyo, Japan) and paraffin-embedded sections of the earlobe specimens were stained with Giemsa. For barrier dysfunction, transepidermal water loss (TEWL) on the dorsal side of earlobe was measured using a Mobile Tewameter (Courage + Khazaka Electronic GmbH, Köln, Germany).

Scratching Behavior

The number of scratching bouts with hind paws was determined by using the MicroAct system (Neuroscience Inc., Tokyo, Japan) [30, 31]. At least 2 days or generally a week before the beginning of the treatment with SDS or antigens, polytetrafluoroethylene (Teflon)-coated cylindrical magnet (diameter: 1 mm, length: 3 mm) was subcutaneously implanted into each of both insteps of lightly anesthetized mice and small incisions were sealed by instant glue (Aron Alpha A; Sankyo, Tokyo, Japan). Each mouse was placed in an acryl chamber with chips of wood as bedding at the bottom, which was surrounded by a detection coil set at 6-cm height (midline: 7.5-cm height) to detect motion of the implanted magnets (gain: 2). After waiting for 20–30 min for habituation, the measurement was started to continue for 45–90 min as indicated in the Figures. Scratching bouts were determined by the software (ANIMA; Takeda LabDesign, Ibaraki, Japan), the parameters used for which were empirically optimized. In the setting of parameters, the apparatus detected consecutive scratching behavior consisting of four or more strokes to omit false-positive signals. Parameters typically used in the present study are as follows: peak range: 0.03–0.7 V, P-P range 0.05–1 V, frequency range 8–35 Hz, beats range 4–1,000, duration range 0.1–100 s, form factor range 0–1.35, area range 0.01–1, gap filling limit 0.1 s. In initial preliminary experiments, experimental results were also confirmed by another system for image analysis (SCLABA-Real; Noveltec, Hyogo, Japan) [32].

H1-Antihistamine Administration

The stock solution of an H1-antihistamine, fexofenadine [33], dissolved in DMSO (30 mg/mL), was stored at −80°C until use, and was thawed and diluted with saline (3 mg/mL) before use. Mice were intraperitoneally injected with the fexofenadine dilution or vehicle (10% DMSO in saline) (0.6 mg/0.2 mL/mouse). 30 min later, the measurement of scratching behavior was started. In the days without the measurement, fexofenadine was not administered or was administered intraperitoneally or subcutaneously as indicated in the Figure legend.

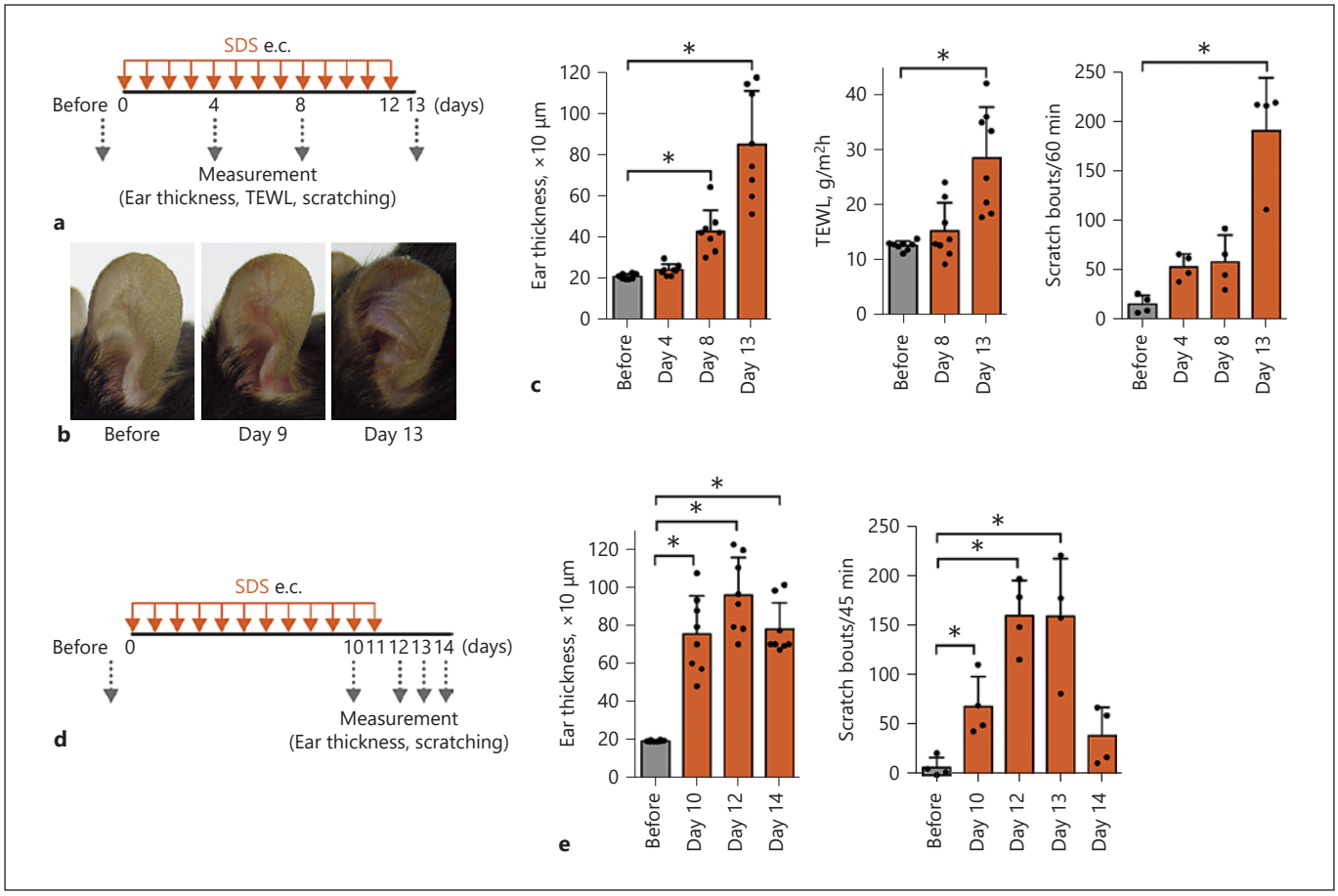

Fig. 1. SDS treatment of ear skin induced ear swelling, barrier dysfunction and itch in C57BL/6 mice. **a** Time line for **b** and **c**. **b** Appearance. **c** Ear thickness, TEWL and hind-paw scratching behavior for 60 min. **d** Time line for **e**. **e** Ear thickness and hind-paw scratching behavior for 45 min. Counts of scratching bouts consisting of four or more strokes were shown as the scratching behavior data. Data indicate the means ± SD. Data are representative of two or more independent experiments with similar results. *p < 0.05 by ANOVA with Tukey's post hoc test. SDS e.c., epicutaneous treatment of earlobe skin with SDS.

Induction of Scratching Behavior by Intradermal Histamine Injection

The nape of neck of mice was shaved. In the next day, 30 min after the intraperitoneal administration with fexofenadine or vehicle, itching was induced by intradermal injection of histamine dihydrochloride (Wako) into the nape of neck without anesthetization (200 μg in 50 μL saline/site, 1.07 μmol/site) [34]. Just after the histamine injection, the measurement of scratching behavior was started.

Quantitative Real-Time PCR

Earlobes excised were subjected to real-time quantitative PCR [13, 35]. The mRNA levels were indicated as relative values to gene expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Flow Cytometry

In the detection of T cell and innate lymphoid cell (ILC) subsets, skin draining cervical lymph node (DLN) cells were counted and the cell surface was stained with FITC-conjugated anti-mouse CD3 (clone 145-2C11) (BioLegend), anti-mouse/human CD44 (clone IM7) (BioLegend), PE-conjugated anti-mouse CD8α (clone 53–6.7) (BD), APC-conjugated anti-mouse CD8α (clone 53–6.7) (BioLegend), anti-mouse CD25 (clone PC61) (BioLegend), PerCP-Cy5.5-conjugated anti-mouse CD4 (clone: RM4-5) (BD), PE-Cy7-conjugated anti-mouse lineage markers (B220 [clone RA3-6B2] [BD], CD3 [clone 145-2C11], CD11b [clone M1/70], Ter119 [clone TER-119], CD49b [clone DX5], FcεRIα [clone MAR-1] [BioLegend], CD16/CD32 [clone 2.4G2] [TONBO], CD14 [clone Sa2-8] [Thermo Fisher], and CD11c [clone N418] [invitrogen]), biotinylated anti-mouse T1/ST2 (clone DJ8) (MD Bioproducts, Zürich, Switzerland), and streptavidin-PE (BD). After surface staining, washing, fixation, and permeabilization with True-Nuclear Transcription Factor Buffer Set (BioLegend), intracellular GATA-3, RORγt, T-bet, and FOXP3 were stained with eFluor 660-conjugated anti-mouse GATA-3 (clone TWAJ) (invitrogen) or eFluor 660-conjugated rat IgG2b isotype control (Thermo Fisher), APC-conjugated anti-mouse RORγt (clone B2D) (invitrogen) or APC-conjugated rat IgG1, PE-conjugated anti-human/mouse T-bet (clone 4B10) (BioLegend) or PE-conju-

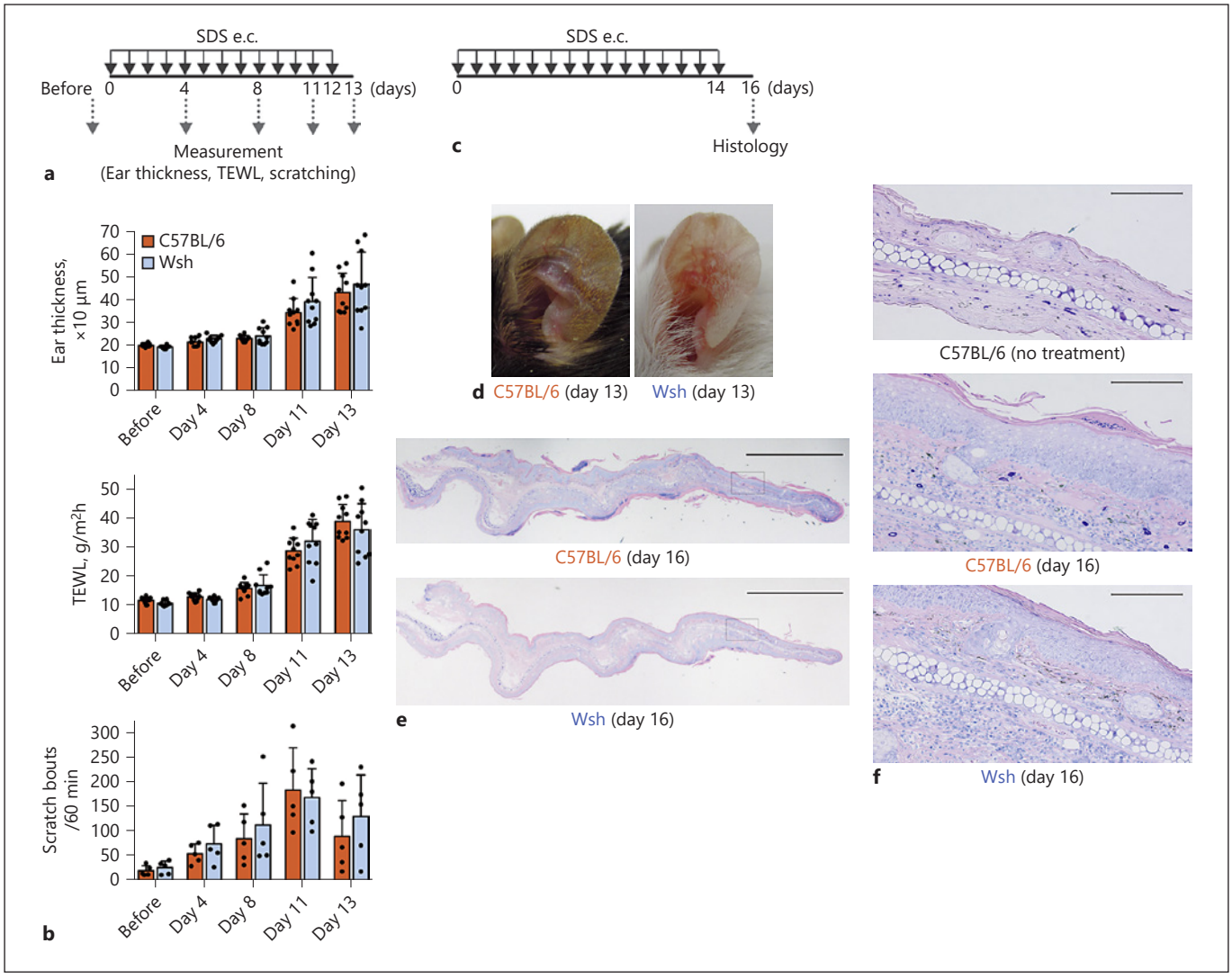

Fig. 2. SDS-inducible itch-associated skin inflammation was equivalent between wild-type and mast cell-deficient mice on the C57BL/6 genetic background. **a** Time line for **b**. **b** Ear thickness, TEWL, and hind-paw scratching behavior for 60 min. **c** Time line for **d**–**f**. **d** Appearance. **e**, **f** Histology. Giemsa stained paraffin sections of earlobes. Bar = 2 mm (**e**) and 125 μm (**f**). Counts of scratching bouts consisting of four or more strokes were shown as the scratching behavior data. Data indicate the means ± SD. Data are representative of two or more independent experiments with similar results. There are no statistical differences by the Mann-Whitney U test between C57BL/6 (wild-type) and mast cell-deficient mice on the C57BL/6 genetic background (Wsh). SDS e.c., epicutaneous treatment of earlobe skin with SDS.

gated mouse IgG1 isotype control (BioLegend), PE-conjugated anti-mouse Foxp3 (clone MF14) (BioLegend) or PE-conjugated rat IgG2b isotype control (BD). Acquisition and analysis were performed using a FACSVerse cell sorter (BD, Franklin Lakes, NJ, USA) and FlowJo software (BD).

Statistical Analysis

One-way ANOVA with the Tukey post hoc test, Student's *t* test (two-tailed) or the Mann-Whitney U test (two-tailed) was used as indicated in the figure legends. A value of $p < 0.05$ was regarded as statistically significant.

Results

SDS Treatment of Ear Skin Induced Skin Inflammation, Barrier Dysfunction, and Itch in C57BL/6 Mice

Administration of 10% SDS to ear skin of C57BL/6 mice every day for approximately 2 weeks induced skin inflammation with gradual increases of ear thickness, TEWL, and hind-paw scratching behaviors, the last of which is considered to be induced by itch sensation [25]

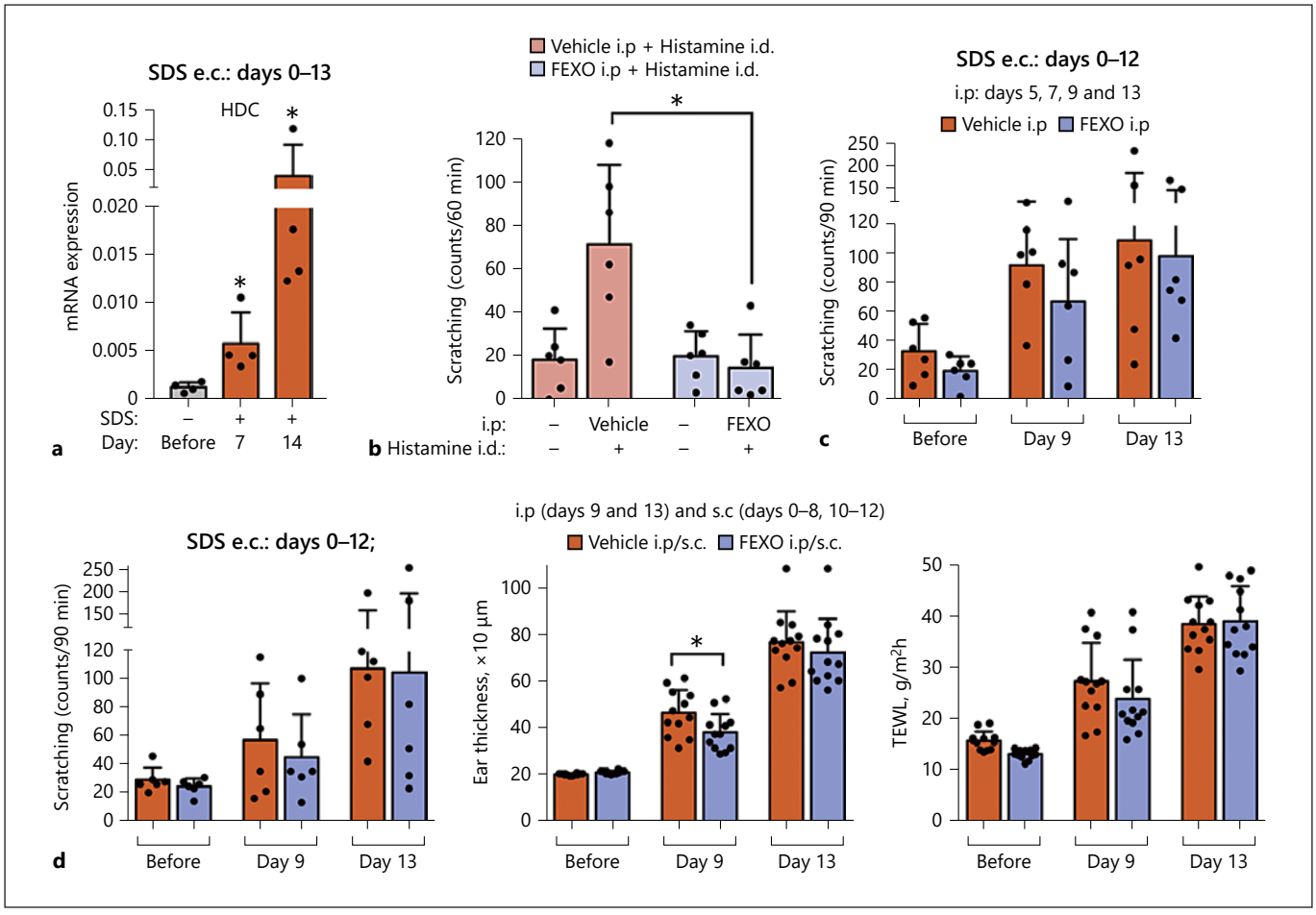

Fig. 3. SDS-inducible itch in C57BL/6 mice was refractory to treatment with an H1 histamine receptor antagonist. **a** qPCR for the gene transcript for L-HDC in murine earlobes treated daily with SDS. **b** Effect of intraperitoneal administration with an H1 histamine receptor antagonist, fexofenadine, on hind-paw scratching behavior induced by intradermal histamine injection. Naïve mice were preadministered with vehicle or fexofenadine 30 min before the histamine injection into the neck of nape. The 60 min measurement was started immediately after the histamine injection. **c** Scratching behavior in SDS-treated mice with intraperitoneal administration of fexofenadine on days 5, 7, 9, and 13. Murine earlobes were daily treated with SDS. Mice were administered with vehicle or fexofenadine 30 min before the 90 min measurement. **d** Scratching behaviors, ear thickness, and TEWL in SDS-treated mice with intraperitoneal (days 9 and 13) and subcutaneous administration into right or left lower back with fexofenadine (days 0–8 and 10–12). Data indicate the means ± SD. Data are representative of two or more independent experiments with similar results except for ear thickness in **d**, where the statistically significant difference in ear thickness on day 9 was observed in two out of four independent experiments. Counts of scratching bouts consisting of four or more strokes were shown as the scratching behavior data. *$p < 0.05$ by the Mann-Whitney U test. SDS e.c., epicutaneous treatment of earlobe skin with SDS; i.p., intraperitoneal administration; i.d., intradermal administration; s.c., subcutaneous administration; FEXO, fexofenadine; HDC, histidine decarboxylase; qPCR, quantitative PCR.

(Fig. 1a–c). The peak value of scratching bouts retained at least 48 h after the last SDS treatment and some mice showed the increased scratching bouts even longer (Fig. 1d, e).

SDS-Inducible Itch-Associated Skin Inflammation Was Equivalent between Wild-Type and Mast Cell-Deficient Mice on the C57BL/6 Genetic Background

The SDS-inducible responses were compared between wild-type and mast cell-deficient Wsh mice on the C57BL/6 genetic background. The mast cell-deficiency did not show decrease of the responses of ear swelling, barrier dysfunc-

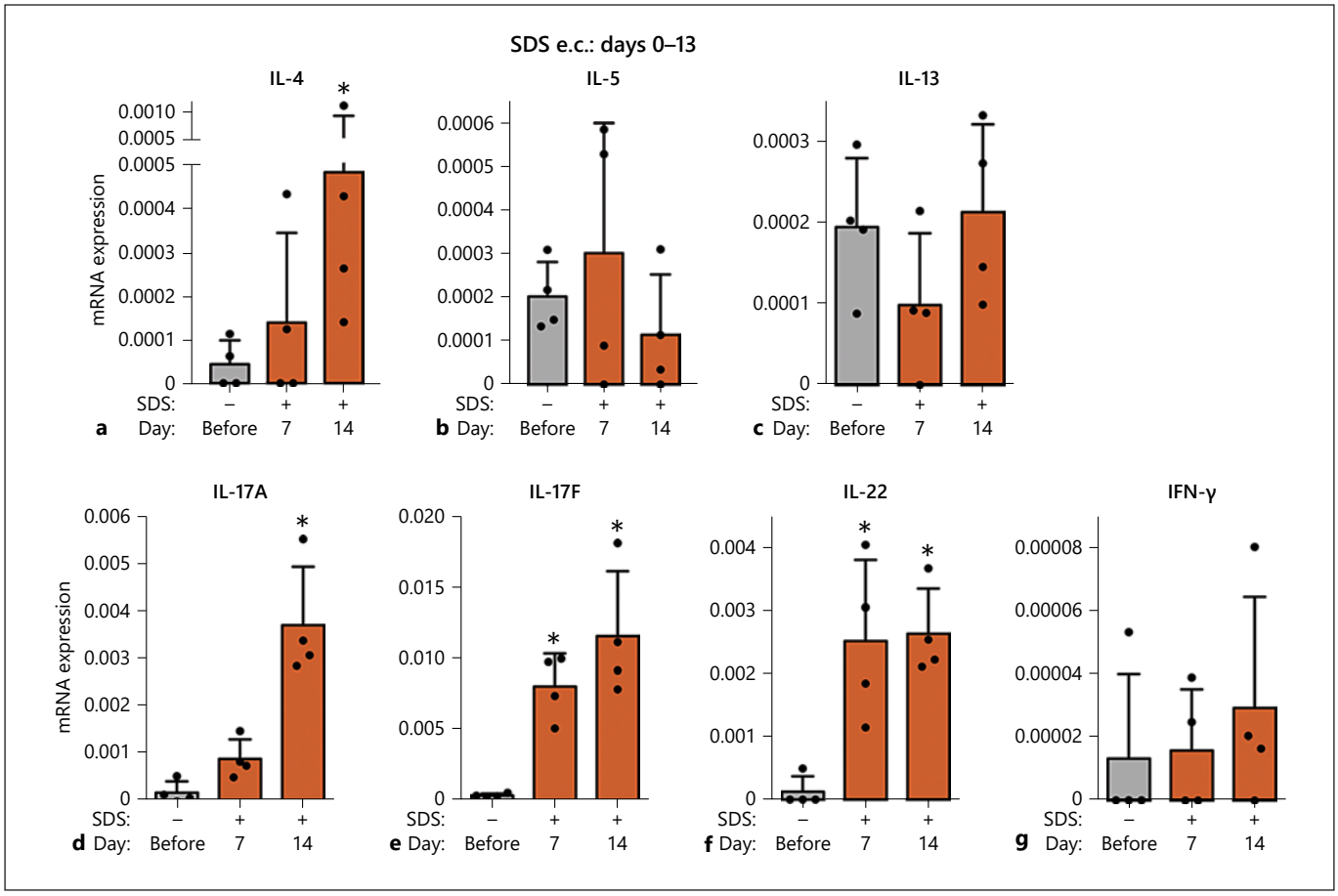

Fig. 4. a–g SDS-inducible itch-associated skin inflammation in C57BL/6 mice was associated with upregulated gene expression of IL-4, IL-17A, IL-17F, and IL-22. qPCR for Th cytokine genes. Data indicate the means ± SD. Data are representative of two or more independent experiments with similar results. *$p < 0.05$ versus *Before* by the Mann-Whitney U test. SDS e.c., epicutaneous treatment of earlobe skin with SDS; qPCR, quantitative PCR.

tion, and itch nor impairment of dermatitis in the appearance of earlobes (Fig. 2a–d). Histology showed epidermal hyperplasia and swelling of dermis with neutrophilic inflammation in the mast cell-sufficient or deficient mice (Fig. 2e, f).

SDS-Inducible Itch in C57BL/6 Mice Was Refractory to Treatment with an H1 Histamine Receptor Antagonist

The SDS treatment of C57BL/6 mice induced upregulation of gene expression of the gene for L-histidine carboxylase, which is responsible to the production of histamine (Fig. 3a).

In mice untreated with SDS, intradermal injection of histamine dihydrochloride into the nape of neck (0.2 mg/site, 1 μmol/site) immediately induced hind-paw scratching behavior in mice, which were preadministered intraperitoneally with vehicle 30 min before the measurement, but did not in mice preadministered with an H1-antihistamine, fexofenadine (Fig. 3b, online suppl. Fig. S1; see www.karger.com/doi/10.1159/000525656 for all online suppl. material). The histamine injection appeared to show more frequency of short-term scratching bouts with a few strokes (online suppl. Fig. S1) than the SDS treatment (unpublished observations). However, the same dose of fexofenadine preadministration 30 min before the measurement did not affect the frequency of scratching behaviors (Fig. 3c), differing from the other model with ICR mice that showed impairment of SDS-inducible scratching behavior on treatment with another H1-antihistamine, terfenadine [25]. Even daily subcutaneous or intraperitoneal fexofenadine administration did not af-

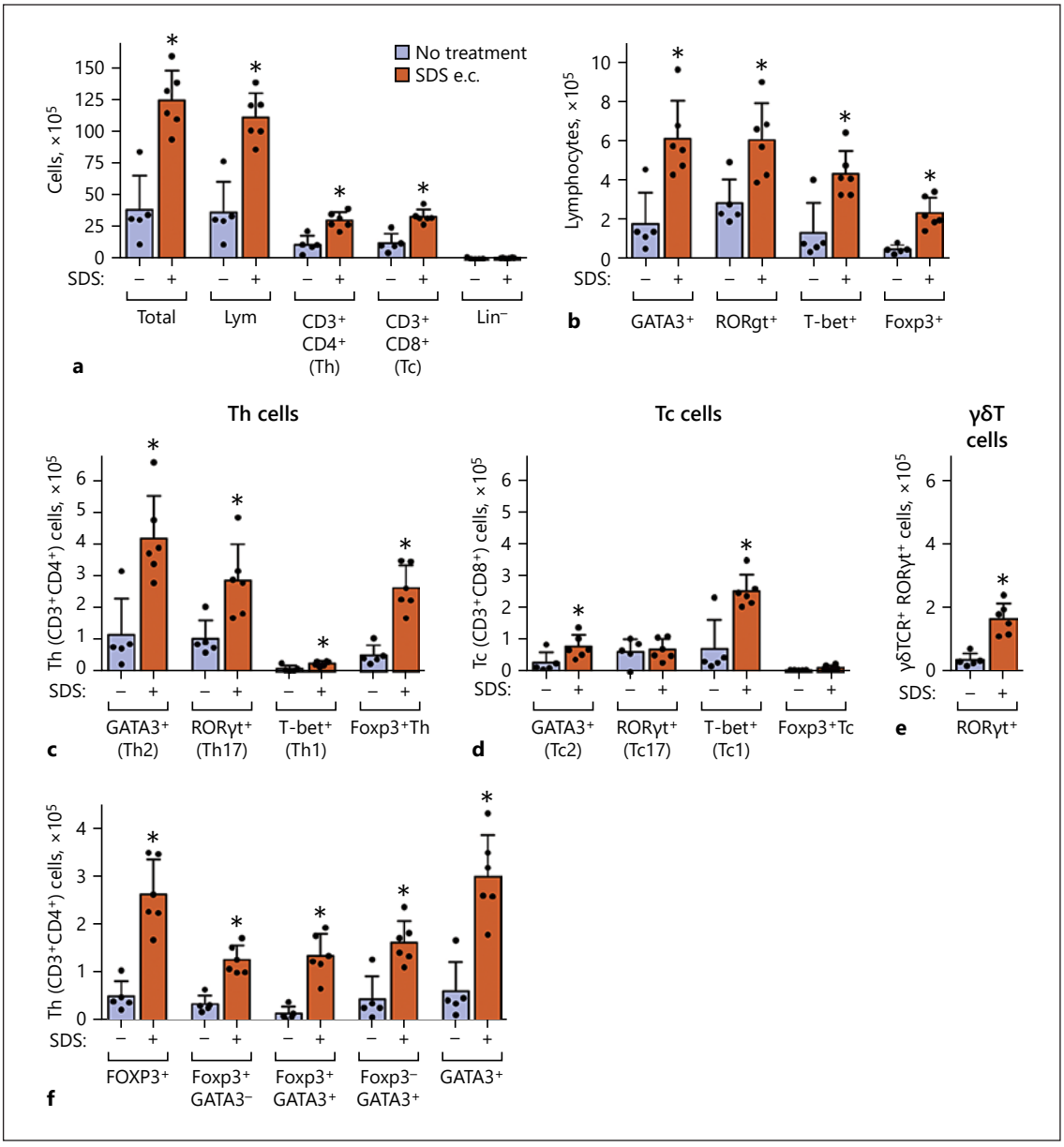

Fig. 5. SDS treatment of ear skin of C57BL/6 mice promoted T cell accumulation in DLNs. DLN cells were analyzed with flow cytometry (day 14). **a** Total cells, lymphocytes, Th ($CD4^+CD3^+$), Tc ($CD8^+CD3^+$) and Lin^-. **b–f** Lymphocytes (**b**), Th ($CD4^+CD3^+$) (**c**, **e**), Tc ($CD8^+CD3^+$) (**d**), and γδT ($\gamma\delta TCR^+CD3^+$) cells (**e**) with enhanced expression of signature transcription factors, GATA3, RORγt, T-bet, and FOXP3. Data indicate the means ± SD. Data are representative of two independent experiments with similar results. *$p < 0.05$ by Student's t test. SDS e.c., epicutaneous treatment of earlobe skin with SDS; Lin^-, lineage-negative cells.

fect the scratching behavior, ear swelling, and TEWL except for slight decrease of ear thickness observed in two out of the four experiments (Fig. 3d).

SDS-Inducible Itch-Associated Skin Inflammation in C57BL/6 Mice Was Associated with Upregulated Gene Expression of IL-4, IL-17A, IL-17F, and IL-22

Interaction between immune and barrier systems and, recently, that between immune and sensory nervous sys-

tems have been reported [27–29, 36–41]. Therefore we analyzed gene expression of Th cytokines in SDS-treated earlobes to find that the SDS treatment induced upregulation of gene expression of Th2 (IL-4 but neither IL-5 nor IL-13) and Th17/Th22 (IL-17A, IL-17F, and IL-22) but not Th1 (IFN-γ) cytokines (Fig. 4).

The SDS Treatment of Ear Skin in C57BL/6 Mice Promoted T Cell Accumulation in DLNs

We next analyzed DLN T cells by flow cytometry (Fig. 5, online suppl. Fig. S2). SDS treatment increased the DLN cell number of total cells, the majority of which are lymphocytes including Th, cytotoxic T (Tc) and γδT cells (Fig. 5a, c–e). Some of these cells showed increased expression levels of signature transcription factors for Th2 (GATA3), Th17 (RORγt), Th1 (T-bet), and Foxp3$^+$ Treg cells (Foxp3) in SDS-treated mice in comparison with untreated mice (Fig. 5b–e). Among them, SDS-treated mice showed increased numbers of GATA3$^+$ Th, RORγt$^+$ Th, Foxp3$^+$ Th (Fig. 5c), GATA3$^+$ Tc, T-bet$^+$ Tc (Fig. 5d), and RORγt$^+$ γδT cells (Fig. 5e) in comparison with untreated mice. GATA3$^+$ Th or Foxp3$^+$ Th cells were composed of nearly equivalent numbers of GATA3$^+$ Foxp3$^-$, GATA3$^+$ Foxp3$^+$, and GATA3$^-$ Foxp3$^+$ Th cells (Fig. 5f).

Discussion

The mechanisms of ICD are poorly understood [6, 7]. We established a novel ICD model of SDS-inducible skin inflammation with itch in mice, earlobe skin of which was treated with 10% SDS for longer than a week (Fig. 1). We used C57BL/6 mice because this inbred strain has been used for analyses for mechanisms in various disease models. The model showed mast cell-independency and, importantly, was refractory to H1-antihistamine administration (Fig. 3). The model would be useful for elucidation of mechanisms for refractory subtypes of itch-associated skin diseases such as atopic dermatitis, psoriasis, contact dermatitis, and so on.

Methodologically, our model has differences in the mouse strain, area, and period used for the SDS treatment from another model established by Inami et al. [25] (ICR mice, shaved back skin, and 4 days, respectively). Unexpectedly, differing from their model [25], our model was refractory to H1-antihistamine administration (Fig. 3c, d). Kuraishi [26] reported that intradermal histamine injection of a dose ten-times lower (0.1 μmol/site) than that used in the present study (Fig. 3b) induced itching effectively in ICR mice but not in the other strains tested including C57BL/6, WBBF1$^{+/+}$ and so on. Thus the C57BL/6 strain appears to be less sensitive to histamine than ICR, i.e., a possible reason for that the present model was H1-antihistamine refractory even though the SDS treatment induced upregulation of gene expression of L-histidine carboxylase consistently with the ICR model [25] (Fig. 3a). We do not exclude a possibility that modifications of the model to regulate expression of genes responsible to histamine production, histamine degradation, or H1 receptor signaling pathways may result in sensitivity to the H1-antihistamine treatment. Neurotransmitters other than histamine and receptors responsible in the present model are yet to be investigated [27–29].

Interaction between immune and barrier systems and that between immune and sensory nervous systems have been reported [27–29, 36–41]. A novel finding in the present study that the SDS treatment induced upregulation of gene expression of a Th2 cytokine IL-4 (Fig. 4a) and Th17/Th22 cytokines (Fig. 4d–f) might suggest contribution of these cytokines to the skin inflammation and/or itch. Candidate cellular sources for these cytokines includes Th2, Th17, Th22, and innate-type cells, such as basophils, ILCs, γδT cells, and so on, which could be skin resident to respond to external stimuli or could be accumulated in DLNs to be delivered to the affected skin. Recent advances in understanding of atopic dermatitis suggest contributions of the Th2 and Th22 cytokine axes to the pathogenesis of the disease and the Th17 cytokine axis to intrinsic, pediatric, and Asian subtypes [8–11]. IL-4 contributes to barrier dysfunction and stimulates sensory neurons amplify or directly induce itching [27–29]. Cellular and molecular mechanisms of contribution of IL-4 and Th17/Th22 cytokines to the present model are yet to be investigated.

SDS treatment promoted accumulation of lymphocytes including Th, Tc, and γδT cells in DLNs, suggesting increased potentials for differentiation and/or activation of these T cell subsets on encounters to antigens, irritants and commensal bacteria (Fig. 5). Increases of cells with enhanced expression of signature transcription factors for a variety of Th and Tc subsets, Th2, Th17, Tc1, and Treg, in SDS-treated mice compared to untreated mice may positively or negatively regulate the model. Interestingly epicutaneous patch administration of 5% or 4% SDS on shaved back skin in mice causes myeloid cell-dependent dermatitis [19–22] or induces IL-33-dependent skin migration of regulatory T cells [24]; however, in these models itch sensation was not reported [19–22] or not inducible [24]. Roles of T cell subsets in the present itch-associated model should be addressed in future studies.

We cannot exclude the possibility of contribution of innate cells such as basophils and ILCs in the skin tissue to the present model.

Results obtained using mast cell-deficient mice on the C57BL/6 genetic background (Fig. 2) are consistent with a report by Inami et al. [25] that mast cell-deficient WBBF1-*W*/*W*^{v} and their normal littermates, WBBF1$^{+/+}$, showed equivalent numbers of scratching bouts in their model with methodological differences in the site and period for SDS treatment from the present model. The WBBF1$^{+/+}$ strain is less sensitive to histamine than ICR [26], although whether the SDS-inducible itch in WBBF1$^{+/+}$ mice is sensitive or refractory to H1-antihistamine treatment is unknown [25].

In conclusions, the present study showed that SDS treatment of ear skin in C57BL/6 mice induces mast cell-independent skin inflammation with H1-antihistamine-refractory itch and suggested a possible Th cytokine (IL-4, IL-17A, IL-17F, and IL-22)- and/or lymphocyte-mediated regulation of the model. The model would be useful for elucidation of mechanisms for detergent-induced ICD with H1-antihistamine-refractory itch.

Acknowledgments

We thank Misaki Mochida, Saki Kazaana, Yoko Morita, Mayuna Imai, and Yuri Otsuka (Japan Women's University) for their technical assist; Yuji Takeda (Takeda LabDesign) and Eriko Komiya (JIRC) for technical advice for the MicroAct/ANIMA analysis and the SCLABA analysis, respectively; Toyoko Hidano, Fumio Kanai, and Norihiro Tada (Juntendo University Graduate School of Medicine) for animal care; the staff of the Laboratory of Morphology and Image Analysis of Juntendo University Graduate School of Medicine for specimen preparation for histology; and Michiyo Matsumoto and Emi Yamaguchi for their secretarial assistance.

Statement of Ethics

The animal experiments were approved by the Committee on Animal Experiments of Juntendo University School of Medicine (approval numbers: 20221187, 2021022, 2020244, 310039, and 3000066) and conducted according to the guidelines of the committee.

Conflict of Interest Statement

The authors state no conflicts of interest.

Funding Sources

This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Nos. JP22K08529 and JP18K08417).

Author Contributions

Yurie Masutani and Toshiro Takai wrote the original draft of the manuscript. Toshiro Takai organized the study. Yurie Masutani, Toshiro Takai, Seiji Kamijo, Saori Ichikawa, Toru Kimitsu, Tomoko Yoshimura, Saya Shimizu, Takasuke Ogawa, and Keiko Takada performed the experiments, analyzed the data, and/or interpreted the data. Toshiro Takai contributed to the total study design and edited the manuscript. Yurie Masutani, Seiji Kamijo, Saori Ichikawa, Mitsutoshi Tominaga, Hajime Suto, Kenji Takamori, Hideoki Ogawa, Ko Okumura, and Shigaku Ikeda also contributed to design of the study and/or reviewing and editing of the manuscript. All the authors approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author and its online supplementary material.

References

1 Van der Valk PGM, Maibach HI. Post-application occlusion substantially increases the irritant response of the skin to repeated short-term sodium lauryl sulfate (SLS) exposure. Contact Dermatitis. 1989;21(5):335–8.
2 de Jongh CM, Lutter R, Verberk MM, Kezic S. Differential cytokine expression in skin after single and repeated irritation by sodium lauryl sulphate. Exp Dermatol. 2007;16(12):1032–40.
3 Angelova-Fischer I, Becker V, Fischer TW, Zillikens D, Wigger-Alberti W, Kezic S, et al. Tandem repeated irritation in aged skin induces distinct barrier perturbation and cytokine profile in vivo. Br J Dermatol. 2012;167(4):787–93.
4 Xian M, Wawrzyniak P, Rückert B, Duan S, Meng Y, Sokolowska M, et al. Anionic surfactants and commercial detergents decrease tight junction barrier integrity in human keratinocytes. J Allergy Clin Immunol. 2016;138(3):890–3.e9.
5 Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. J Allergy Clin Immunol. 2020;145(6):1517–28.
6 Scheinman PL, Vocanson M, Thyssen JP, Johansen JD, Nixon RL, Dear K, et al. Contact dermatitis. Nat Rev Dis Primers. 2021;7(1):38.
7 Johansen JD, Bonefeld CM, Schwensen JFB, Thyssen JP, Uter W. Novel insights into contact dermatitis. J Allergy Clin Immunol. 2022;149(4):1162–71.
8 Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139(4):S65–s76.
9 Ahn K, Kim BE, Kim J, Leung DY. Recent advances in atopic dermatitis. Curr Opin Immunol. 2020;66:14–21.

10 Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143:1–11.
11 Tokura Y, Hayano S. Subtypes of atopic dermatitis: from phenotype to endotype. Allergol Int. 2022;71(1):14–24.
12 Malik K, Ungar B, Garcet S, Dutt R, Dickstein D, Zheng X, et al. Dust mite induces multiple polar T cell axes in human skin. Clin Exp Allergy. 2017;47(12):1648–60.
13 Shimura S, Takai T, Iida H, Maruyama N, Ochi H, Kamijo S, et al. Epicutaneous allergic sensitization by cooperation between allergen protease activity and mechanical skin barrier damage in mice. J Invest Dermatol. 2016;136(7):1408–17.
14 Suchiva P, Takai T, Kamijo S, Maruyama N, Yokomizo T, Sugimoto Y, et al. Inhibition of both cyclooxygenase-1 and -2 promotes epicutaneous Th2 and Th17 sensitization and allergic airway inflammation on subsequent airway exposure to protease allergen in mice. Int Arch Allergy Immunol. 2021;182(9):788–99.
15 Kunimine S, Takai T, Kamijo S, Maruyama N, Kimitsu T, Masutani Y, et al. Epicutaneous vaccination with protease inhibitor-treated papain prevents papain-induced Th2-mediated airway inflammation without inducing Th17 in mice. Biochem Biophys Res Commun. 2021;546:192–9.
16 Ogasawara A, Yuki T, Takai T, Yokozeki K, Katagiri A, Takahashi Y, et al. Epicutaneous challenge with protease allergen requires its protease activity to recall T(H)2 and T(H)17/T(H)22 responses in mice pre-sensitized via distant skin. J Immunotoxicol. 2021;18(1):118–26.
17 Ochi H, Takai T, Shimura S, Maruyama N, Nishioka I, Kamijo S, et al. Skin treatment with detergent promotes protease allergen-dependent epicutaneous sensitization in a manner different from tape stripping in mice. J Invest Dermatol. 2017;137(7):1578–82.
18 Muto T, Fukuoka A, Kabashima K, Ziegler SF, Nakanishi K, Matsushita K, et al. The role of basophils and proallergic cytokines, TSLP and IL-33, in cutaneously sensitized food allergy. Int Immunol. 2014;26(10):539–49.
19 Heijnen IA, van Vugt MJ, Fanger NA, Graziano RF, de Wit TP, Hofhuis FM, et al. Antigen targeting to myeloid-specific human Fc gamma RI/CD64 triggers enhanced antibody responses in transgenic mice. J Clin Invest. 1996;97(2):331–8.
20 Thepen T, van Vuuren AJH, Kiekens RCM, Damen CA, Vooijs WC, van de Winkel JGJ, et al. Resolution of cutaneous inflammation after local elimination of macrophages. Nat Biotechnol. 2000;18(1):48–51.
21 Kim C, Sano Y, Todorova K, Carlson BA, Arpa L, Celada A, et al. The kinase p38 alpha serves cell type-specific inflammatory functions in skin injury and coordinates pro- and anti-inflammatory gene expression. Nat Immunol. 2008;9:1019–27.
22 Hristodorov D, Mladenov R, Fischer R, Barth S, Thepen T. Fully human MAP-fusion protein selectively targets and eliminates proliferating CD64(+) M1 macrophages. Immunol Cell Biol. 2016;94(5):470–8.
23 Hayashi S, Ishikawa S, Ishii E, Koike M, Kaminaga T, Hamasaki Y, et al. Anti-inflammatory effects of potassium iodide on SDS-induced murine skin inflammation. J Invest Dermatol. 2020;140(10):2001–8.
24 Toyama S, Moniaga CS, Nakae S, Kurosawa M, Ogawa H, Tominaga M, et al. Regulatory T cells exhibit interleukin-33-dependent migratory behavior during skin barrier disruption. Int J Mol Sci. 2021;22(14):7443.
25 Inami Y, Sasaki A, Andoh T, Kuraishi Y. Surfactant-induced chronic pruritus: role of L-histidine decarboxylase expression and histamine production in epidermis. Acta Derm Venereol. 2014;94(6):645–50.
26 Kuraishi Y. Methods for preclinical assessment of antipruritic agents and itch mechanisms independent of mast-cell histamine. Biol Pharm Bull. 2015;38(5):635–44.
27 Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. J Allergy Clin Immunol. 2018;142(5):1375–90.
28 Yang TLB, Kim BS. Pruritus in allergy and immunology. J Allergy Clin Immunol. 2019;144(2):353–60.
29 Steinhoff M, Ahmad F, Pandey A, Datsi A, AlHammadi A, Al-Khawaga S, et al. Neuroimmune communication regulating pruritus in atopic dermatitis. J Allergy Clin Immunol. 2022;149(6):1875–98.
30 Inagaki N, Igeta K, Shiraishi N, Kim JF, Nagao M, Nakamura N, et al. Evaluation and characterization of mouse scratching behavior by a new apparatus, MicroAct. Skin Pharmacol Appl Skin Physiol. 2003;16(3):165–75.
31 Takahashi S, Ishida A, Kubo A, Kawasaki H, Ochiai S, Nakayama M, et al. Homeostatic pruning and activity of epidermal nerves are dysregulated in barrier-impaired skin during chronic itch development. Sci Rep. 2019;9(1):8625.
32 Noguchi A, Tominaga M, Takahashi N, Matsuda H, Kamata Y, Umehara Y, et al. Differences in therapeutic effects of topically applied corticosteroid and tacrolimus on atopic dermatitis-like symptoms in NC/Nga mice. J Dermatol Sci. 2017;86(1):54–62.
33 Simons FER, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. J Allergy Clin Immunol. 2011;128(6):1139–50.e4. e1134
34 Barry DM, Liu XT, Liu B, Liu XY, Gao F, Zeng X, et al. Exploration of sensory and spinal neurons expressing gastrin-releasing peptide in itch and pain related behaviors. Nat Commun. 2020;11(1):1397.
35 Kamijo S, Hara M, Suzuki M, Nakae S, Ogawa H, Okumura K, et al. Innate IL-17A enhances IL-33-independent skin eosinophilia and IgE response on subcutaneous papain sensitization. J Invest Dermatol. 2021;141(1):105–13.e14. e114
36 Akdis CA, Arkwright PD, Brüggen MC, Busse W, Gadina M, Guttman-Yassky E, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75(7):1582–605.
37 Misery L, Brenaut E, Pierre O, Le Garrec R, Gouin O, Lebonvallet N, et al. Chronic itch: emerging treatments following new research concepts. Br J Pharmacol. 2021;178(24):4775–91.
38 Bağci IS, Ruzicka T. IL-31: a new key player in dermatology and beyond. J Allergy Clin Immunol. 2018;141(3):858–66.
39 Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan ZNA, Voisin T, et al. Substance P release by sensory neurons triggers dendritic cell migration and initiates the type-2 immune response to allergens. Immunity. 2020;53(5):1063–77.e7. e1067
40 Serhan N, Basso L, Sibilano R, Petitfils C, Meixiong J, Bonnart C, et al. House dust mites activate nociceptor-mast cell clusters to drive type 2 skin inflammation. Nat Immunol. 2019;20(11):1435–43.
41 Takai T, Ikeda S. Barrier dysfunction caused by environmental proteases in the pathogenesis of allergic diseases. Allergol Int. 2011;60(1):25–35.