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Alloferon and IL-22 receptor expression regulation on the pathogenesis of imiquimod-induced psoriasis

Tomoyo Agura[1,5], Hyejung Jo[1,5], Seulgi Shin[2], Yoojin Jang[1], Chong Won Choi[4], In Su Gwak[1], Jae Seung Kang[1,2,3]✉ & Yejin Kim[1,2]✉

Psoriasis is an immune-mediated inflammatory skin disease. IL-22, a proinflammatory cytokine, is implicated in psoriasis pathogenesis; however, there is currently no established biological treatment targeting IL-22 or its receptor, IL-22Rα. Alloferon is a short peptide that has an antiinflammatory effect on skin disorders; however, little is known about its anti-inflammatory activity in psoriasis. We investigated the regulatory role of alloferon in the development of psoriasis in an imiquimod (IMQ)-induced psoriasis model through the regulation of IL-22Rα expression. The expression of IL-22Rα was analyzed by immunofluorescence staining in primary human keratinocytes. The effect of alloferon on the development of psoriasis was investigated in IMQ-induced wild-type and IL-22Rα KO mice. We found that alloferon decreased the expression of IL-22Rα in psoriasis-like keratinocytes treated with TNF-α, while epidermal hyperplasia was observed in IMQ-induced wild-type and IL-22Rα KO mice. In addition, the expression of IL-1β, IL-19, and IL-33 was suppressed when IL-22Rα KO mice were treated with alloferon. The findings of this study indicate that alloferon could be an effective potential drug for the treatment of psoriasis by interrupting IL-22 signaling and factors related to skin inflammation.

Keywords Interleukin-22 receptor, Psoriasis, Alloferon, Keratinocytes

Psoriasis is a chronic inflammatory skin disease that affects 2–3% of the global population and occurs more frequently with advancing age[1–3]. Psoriasis is an immune-mediated chronic inflammatory skin disease caused by excessively activated T cells infiltrating the skin and stimulating keratinocytes by secreting proinflammatory cytokines[4–6]. Therefore, a possible therapeutic strategy to alleviate the progression of lesions in psoriasis is to regulate keratinocyte proliferation or inflammatory cytokines[7–9]. However, there are limitations in that treatments are highly expensive and are administered to patients through intramuscular or subcutaneous injection, not cream or ointment[10–12]. To compensate for the limitations of biological agents, we focused on alloferon as an adjuvant in the therapy of psoriasis. Alloferon, an immune modulator, is a short peptide isolated from the blood of Calliphora vicina larvae after infection with bacteria[13–15]. In a previous study, it was demonstrated that alloferon inhibits inflammatory responses in skin exposed to UVB through the suppression of the proinflammatory cytokines, IL-1α, IL-1β, IL-6, and IL-18[16].

IL-22 is a proinflammatory cytokine that is structurally related to IL-10[17,18]. IL-22 upregulates pancreatitis-associated protein 1 in pancreatic acinar cells[19] and the production of acute-phase proteins in hepatoma cells[20–22], suggesting its involvement in the inflammatory response. It is known that IL-22 induces the proliferation of keratinocytes, leading to hyperplasia of the epidermis[23–25]. IL-22 plays a role in the pathogenesis of psoriasis[26–28], but a treatment for the regulation of the activity of IL-22 has not yet been developed. IL-22 signals through a heterodimeric receptor composed of two chains, the IL-22Rα subunit and the IL-10Rβ chain[29–31]. IL-10Rβ is expressed everywhere, but IL-22Rα is widely expressed in nonhematopoietic cells such as the pancreas, liver, and epidermis[28,32]. Thus, to control the biological process of IL-22, it is necessary to regulate the expression

[1]Laboratory of Vitamin C and Antioxidant Immunology, Department of Anatomy and Cell Biology, Seoul National University College of Medicine, Seoul 03080, Republic of Korea. [2]Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul 03080, Republic of Korea. [3]Department of Applied Bioengineering, Graduate School of Convergence Science and Technology, Seoul National University, Seoul 08826, Republic of Korea. [4]Department of Dermatology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam 13620, Republic of Korea. [5]Tomoyo Agura and Hyejung Jo contributed equally to this work. ✉email: genius29@snu.ac.kr; bbambaya921@snu.ac.kr

of IL-22Rα. In this study, we show that downregulation of the expression of IL-22Rα using alloferon, an anti-inflammatory agent, leads to a significant decrease in psoriatic disease severity: inflammation related factors were significantly reduced in imiquimod (IMQ)-induced psoriasis IL-22R KO mice treated with alloferon. Our findings demonstrate that alloferon could be a novel therapeutic strategy for the treatment of psoriasis.

Results

Alloferon decreases the expression of IL-22Rα in TNF-α induced psoriasis-like model in HaCaT and primary human keratinocytes

Although several cytokines, such as TNF-α, IFN-γ, IL-23, and IL-17, are involved in psoriasis pathology[4,33,34], TNF-α plays a particularly important role. In various previous studies, TNF-α has been used to stimulate the human keratinocyte cell line HaCaT and primary human keratinocytes to establish a psoriasis-like model[35–37]. Therefore, we investigated IL-22Rα expression in a TNF-α-treated psoriasis-like cell model using HaCaT cells and primary human keratinocytes in the presence or absence of alloferon. The TNF-α and alloferon used in these experiments were not toxic to keratinocytes (Supplementary Fig. S1).

We found that IL-22Rα expression was increased in TNF-α-treated HaCaT cells compared with in the control, and this increase was suppressed when the cells were simultaneously treated with alloferon (Fig. 1a). The same results were obtained in primary human keratinocytes (Fig. 1b). The relative fluorescence intensity was measured using Celleste Imaging Software and is presented as a graph in Fig. 1c and d.

Alloferon alleviates psoriatic symptoms in an IMQ-induced psoriasis mouse model

Based on previous results regarding the anti-inflammatory effect of alloferon on skin disease, we examined the therapeutic effect of alloferon on psoriasis in an IMQ-induced psoriasis mouse model. Six hours after IMQ treatment, ICR mice were topically applied with alloferon on the shaved dorsal skin and ears for 7 days. The experimental scheme is shown in Fig. 2a. It was observed that psoriasis accompanied by redness and scales was severely induced by IMQ treatment. However, the psoriatic symptoms were remarkably suppressed by alloferon treatment (Fig. 2b).

Next, we examined the histological changes after alloferon treatment on IMQ-induced psoriatic skin lesions using H&E staining. We found that the epidermal thickness of the dorsal skin was increased with IMQ treatment (86.16 ± 13.21 μm) compared with that of control mice (19.63 ± 3.30 μm). However, the thickness of the dorsal skin was dramatically decreased after treatment with alloferon (44.25 ± 4.01 μm) (Fig. 2c and d). As shown in Fig. 2e, IMQ treatment significantly increased the ear thickness, but we could not find any changes with the treatment of alloferon (Fig. 2c and e).

As shown in Fig. 1, alloferon downregulated IL-22Rα expression in TNF-α-induced psoriasis-like HaCaT cells and primary human keratinocytes. Therefore, we examined whether alloferon could also suppress IL-22Rα expression in the skin lesions of IMQ-treated mice. The expression of IL-22Rα is increased by treatment with IMQ, but the increased expression was remarkably suppressed after treatment with alloferon (Fig. 2f). This result suggests that alloferon reduces IMQ-induced hyperproliferation of keratinocytes, a characteristic symptom of psoriasis, through IL-22 signaling.

Patches of thick silvery-white scales are reduced in IMQ-induced IL-22Rα-deficient mice

Because IL-22Rα expression was downregulated and psoriatic symptoms were decreased by treatment with alloferon, we investigated the pathogenesis of psoriasis using IL-22Rα knockout (KO) mice. Scales and plaques were found to be decreased in IMQ-treated IL-22Rα KO mice compared with IMQ-treated wild-type (WT) mice; however, redness remained (Fig. 3a). In addition, H&E staining showed that the dorsal epidermal thickness was reduced in IL-22Rα KO mice compared with WT mice (57.97 ± 7.22 μm in IL-22Rα KO mice vs. 81.24 ± 5.06 μm in WT mice) (Fig. 3b and c). However, ear thickness was not significantly changed in IL-22Rα KO mice compared with WT mice when treated with IMQ (Fig. 3b and d).

Alloferon effectively inhibits IMQ-induced skin inflammation associated with psoriatic symptoms in IL-22Rα-deficient mice

We investigated whether alloferon could have a therapeutic effect on IL-22Ra depletion because alloferon controls IL-22 signaling through the regulation of IL-22Ra in the pathogenesis of psoriasis. Interestingly, alloferon reduced psoriatic symptoms, especially redness, in IL-22Rα KO mice compared with vehicle control mice (Fig. 4a). Furthermore, alloferon treatment effectively decreased the dorsal epidermal thickness and immune cell infiltration (34.02 ± 2.46 μm vs. 60.33 ± 4.19 μm) (Fig. 4b and c). In addition, the ear thickness reflected the results of the changes in the dorsal skin (Fig. 4b and d). Taken together, these results indicate that alloferon cannot prevent the development of psoriasis but is involved in other factors related to the pathogenesis of psoriasis.

Alloferon regulates psoriasis pathogenesis-related genes in IL-22Rα-deficient mice

Microarray analysis was performed to investigate whether alloferon regulated other factors related to psoriasis in the absence of IL-22Rα. Gene ontology analysis was used to sort the data by biological process and identify the top 10 terms of functional classification. Genes related to psoriatic inflammation and pathology, such as the genes encoding β-defensin, IL-1β, S100A7a, IL-33, IL-19, CXCL13, and CXCR6, were upregulated by IMQ treatment, but downregulated by alloferon treatment (Fig. 5a and b). In addition, genes related to skin barriers, such as filaggrin and keratin, were decreased by IMQ administration, but increased by alloferon (Fig. 5c and d). These results indicated that alloferon controls various factors related to skin inflammation and barriers in addition to IL-22R. Therefore, it could be a potential therapeutic agent for inflammatory skin diseases, including psoriasis.

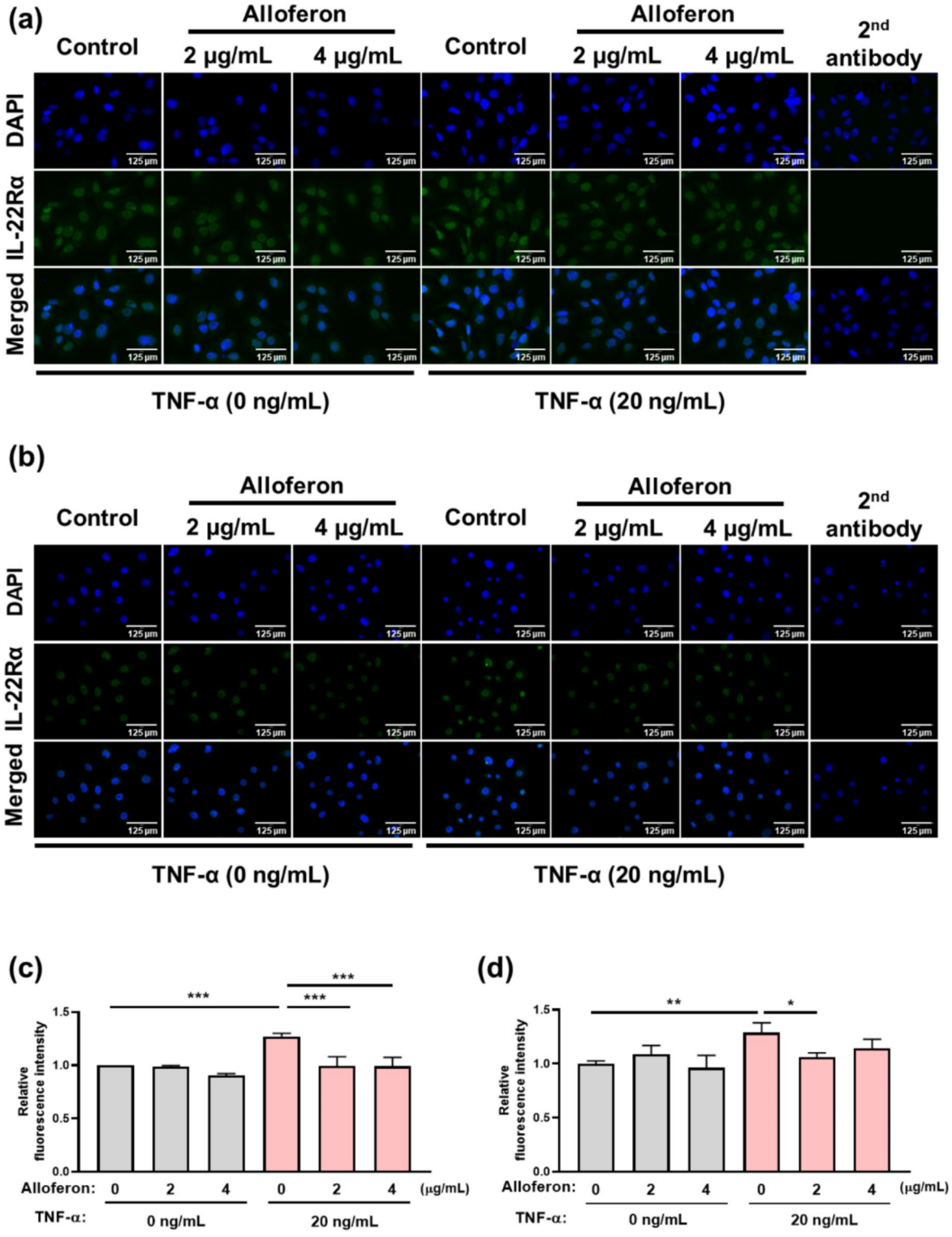


Fig. 1. Alloferon suppresses the expression of IL-22Rα in TNF-α-induced psoriasis-like HaCaT cells and primary human keratinocytes. (a) HaCaT cells and (b) primary human keratinocytes (PHKs) (4×10^4 cells/well) were seeded and treated with 0 or 20 ng/mL of TNF-α for 24 h. Then, alloferon was added at a concentration of 2–4 μg/mL for another 24 h. The expression of IL-22Rα was examined using Alexa Fluor 488 (green) conjugated anti-IL-22Rα antibody as described in the "Materials and methods" section. Nuclei were counterstained with DAPI (blue). Scale bar = 125 μm. (c, d) Relative fluorescence intensity of the expression of IL-22Rα in HaCaT and PHK cells (for a and b). One-way ANOVA with Tukey's multiple comparison test was performed. Data were collected from three independent experiments and presented as the mean ± SD. *** $P < 0.0001$, ** $P < 0.001$, * $P < 0.01$.

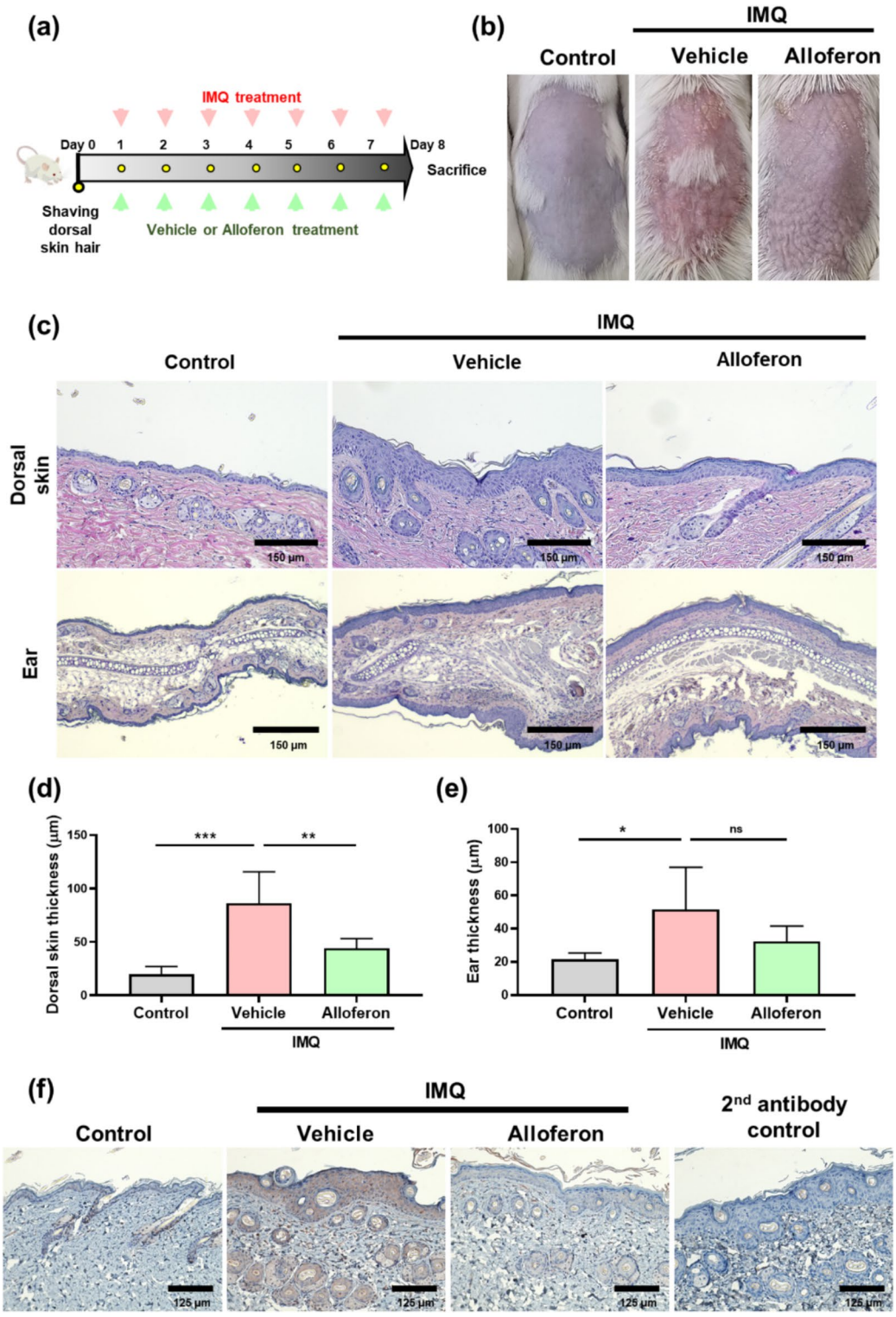


Fig. 2. Alloferon reduces the symptoms of psoriasis through the regulation of IL-22Rα in IMQ-induced psoriatic mice. ICR mice were divided into three groups based on weight ($n = 5$): control + vehicle; IMQ (83.3 mg/day) + vehicle; IMQ (83.3 mg/day) + alloferon (2 μg/mL/day). (a) Experimental schedules. (b) Images were taken on day 7, the last day of the experiment. (c) Dorsal skin and ear sections were stained with H&E. Scale bar = 150 μm. (d, e) Dorsal skin and ear thickness (for c) were measured in three parts per histological section using Celleste 5 software. One-way ANOVA with Tukey's multiple comparisons test was performed; *** $P < 0.0001$, ** $P < 0.001$, * $P < 0.01$, ns; not significant. (f) The expression of IL-22Rα in the skin was analyzed by IHC. Scale bar = 125 μm. Data are representatives of three independent experiments. IMQ, imiquimod; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

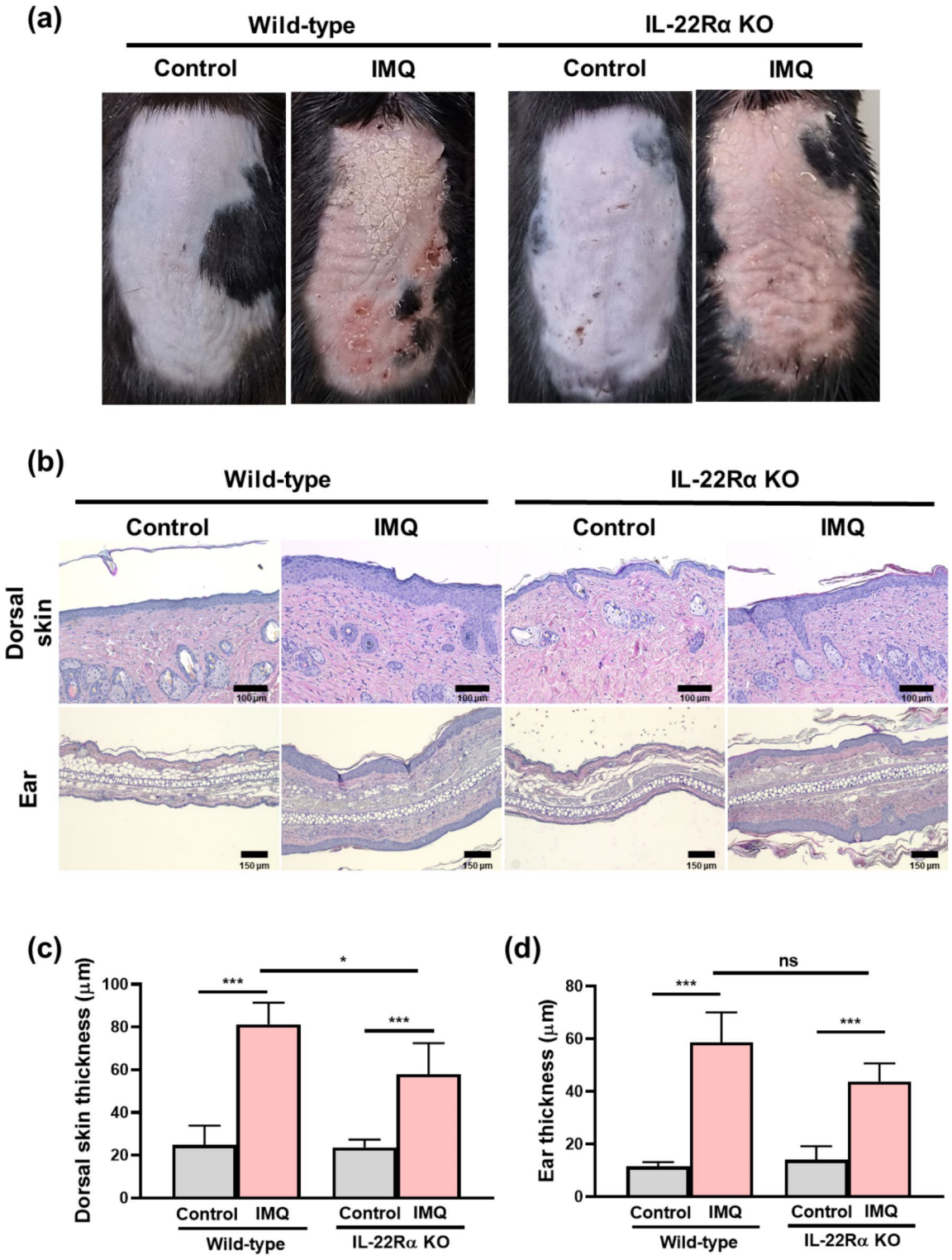


Fig. 3. The symptoms of psoriasis are reduced in IL-22Rα KO mice compared to WT mice. WT and IL-22Rα KO mice (male, 3 months old) were used in this experiment. Mice were divided into four groups ($n = 4$): WT control; WT + IMQ; IL-22Rα KO control; and IL-22Rα KO + IMQ. (a) Representative images were taken on day 7, the last day of the experiment. (b) Dorsal skin and ear tissues were fixed in 4% PFA at 4 °C and sections were stained using H&E. Skin tissue scale bar = 100 µm; ear tissue scale bar = 150 µm. (c, d) The epidermal thickness of the dorsal skin and ear skin (for b) were measured in three parts per histological section using Celleste 5 software. Two-way ANOVA with Sidak's multiple comparisons test was performed; *** $P < 0.0001$; * $P < 0.05$; ns, not significant. Data are representatives of three independent experiments. KO, knockout. PFA, paraformaldehyde.

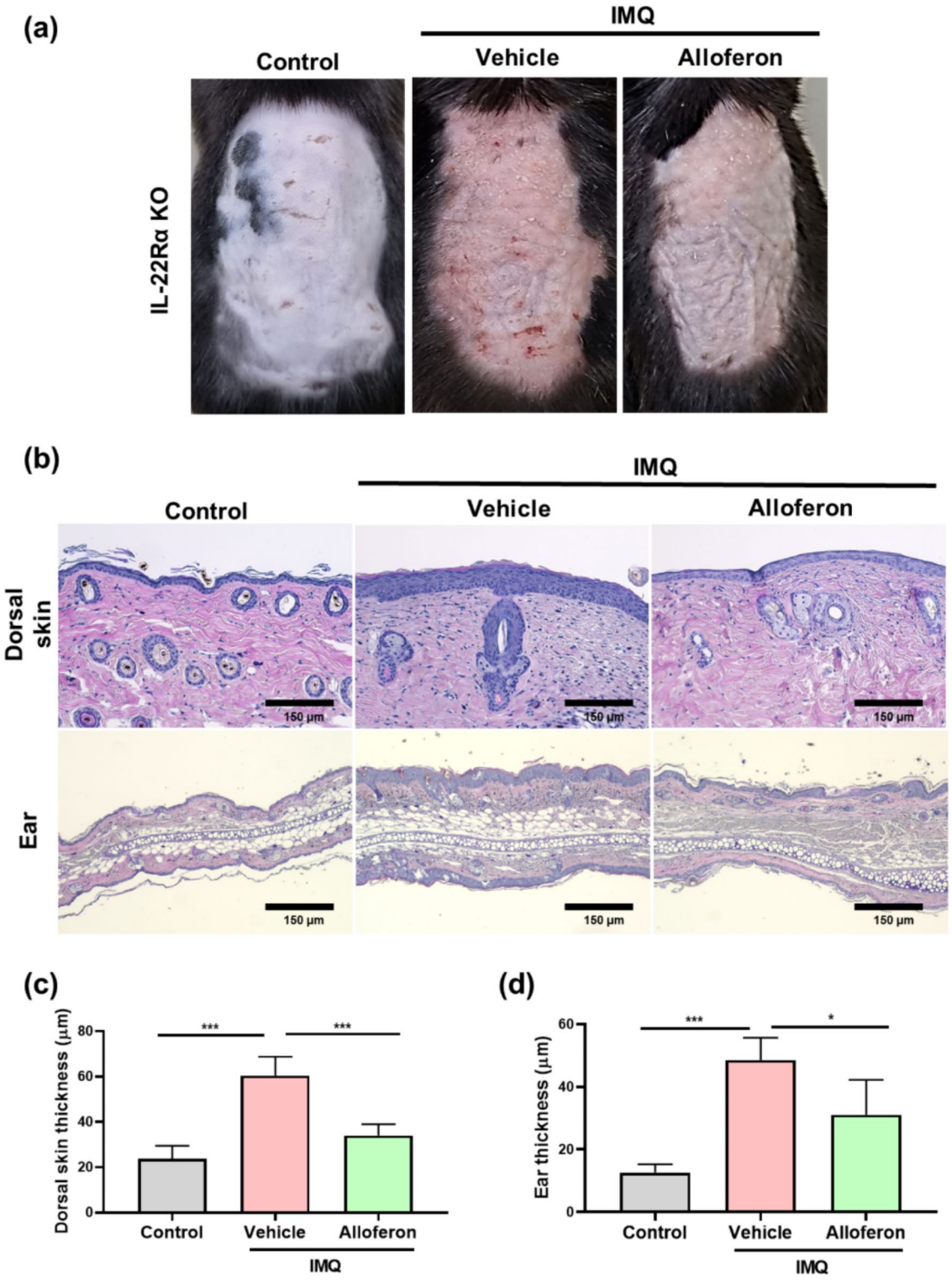
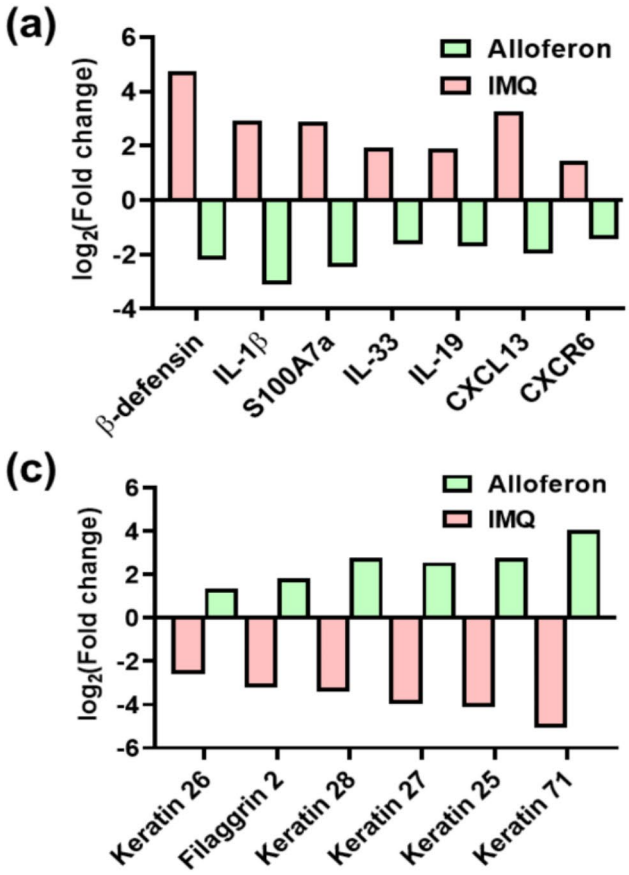


Fig. 4. Alloferon effectively inhibits IMQ-induced skin inflammation related to psoriatic symptoms in IL-22Rα KO mice. IL-22Rα KO mice (male, 3 months old) were used in this experiment. Mice were divided into three groups ($n = 4$): control + vehicle; IMQ + vehicle; IMQ + alloferon (2 μg/mL). (a) Representative images were taken to examine the effect of alloferon on IMQ-induced psoriasis on day 7, the last day of the experiment. (b) Dorsal skin and ear sections were stained using H&E. Scale bar, 150 μm. (c, d) The epidermal thickness of the dorsal skin and ear skin (for b) were measured in three parts per histological section using Celleste 5 software. One-way ANOVA with Tukey's multiple comparison test was performed; *** $P < 0.001$, * $P < 0.01$; ns; not significant. Data are representatives of three independent experiments.



(b)

Gene	Fold change	
	IMQ	Alloferon
β-defensin 3	25.54	-4.54
β-defensin 14	9.84	-2.55
IL-1β	7.62	-8.62
S100A7a	7.37	-5.44
IL-33	3.88	-3.11
IL-19	3.72	-3.28
CXCL13	9.65	-3.9
CXCR6	2.75	-2.73

(d)

Gene	Fold change	
	IMQ	Alloferon
Keratin 26	-2.58	1.35
Filaggrin 2	-3.19	1.84
Keratin 28	-3.41	2.77
Keratin 27	-3.98	2.56
Keratin 25	-4.1	2.78
Keratin 71	-5.07	4.06

Fig. 5. Alloferon regulates psoriasis pathogenesis-related genes in IL-22Rα KO mice. Gene expression in IL-22Rα KO mice treated with IMQ and alloferon was analyzed using Affymetrix GeneChip® Mouse Gene 2.0 ST arrays. Total mRNA was extracted from the dorsal skin as described in the "Materials and methods" section. (a, c) Data are presented as log2 fold change. (b, d) Data are presented as specific number of fold changes in genes.

Discussion

Despite recent advances in the understanding of the pathogenesis of psoriasis and the development of alternative treatment options for patients with psoriasis, precise mediators responsible for maintaining chronic inflammation in psoriatic skin lesions remain unclear. In this study, we focused on IL-22, a key mediator in the pathophysiology of psoriasis[38–40], and alloferon, an immune modulator[41–43]. A previous study demonstrated that exposure to UVB radiation resulted in the induction of inflammation in the skin and the upregulation of IL-22Rα expression in keratinocytes[44]. This implies that the expression level of IL-22R may change in other skin inflammatory environments such as psoriasis and atopic dermatitis. Alloferon has been found to have anti-inflammatory effects on skin inflammation[16]. Our findings revealed that alloferon, which regulates immune-related factors, relieved IL-22R expression in a psoriasis-like in vitro model and an IMQ-induced psoriasis mouse in vivo model. If the expression of the receptor to which IL-22 binds is reduced, the signaling of IL-22 is not initiated; therefore, it is important to regulate the expression of IL-22Rα. This study was conducted on the assumption that alloferon, an immune modulator, would regulate the expression of IL-22Rα to prevent the pathology of psoriasis. The results showed that alloferon reduced increased IL-22Rα expression and alleviated the symptoms of psoriasis; therefore, it was hypothesized that a decrease in IL-22Rα expression would lead to a reduction in psoriatic symptoms. Interestingly, alloferon alleviates the symptoms of psoriasis in IMQ-induced IL-22Rα-deficient mice. As previously mentioned, psoriasis is influenced by various factors, including IL-22 and cytokines such as TNF-α, IL-23, and IL-17[4,6,45], which play roles in inflammation. Therefore, it is evident that the depletion of IL-22Rα alone is insufficient to fully prevent the development of psoriasis, as multiple pathways and factors are involved in its pathogenesis, requiring a more comprehensive approach. Therefore, we investigated whether alloferon alleviated psoriasis by regulating not only the expression of IL-22Rα but also various other factors that cause inflammation in psoriasis, such as IL-1β, IL-19, and IL-33. In particular, IL-19, a member of the IL-10 cytokine family[46,47], is secreted by keratinocytes in response to stimulation by IL-23 and IL-17[48–50], which are involved in the same mechanism as IL-22 in psoriasis[46,51]. IL-19 has been implicated in inducing inflammation in keratinocytes, and active research is currently being conducted on its relevance to psoriasis[45,52].

It is meaningful that alloferon showed an anti-inflammatory effect on psoriasis by regulating the expression of IL-22Rα and genes related to psoriasis inflammation and pathology. These results suggest that alloferon has

therapeutic potential for psoriasis. Currently, biological agents such as Stelara® are being used as treatment options for psoriasis[53,54]. However, these treatments have limitations, including high cost and the need for periodic administration[55]. To address these limitations, a combination therapy approach that involves the coadministration of alloferon and biological agents may be beneficial.

Materials and methods

Cell culture

The human skin keratinocyte cell line HaCaT was provided by Dr. N.E. Fusenig, DKFZ, Heidelberg, Germany. HaCaT cells were maintained in RPMI 1640 medium (WELGENE, Kyungsan, Korea) supplemented with 10% heat-inactivated fetal bovine serum (Gibco, Grand Island, NY, USA) and antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin; WELGENE) at 37 °C in a humidified 5% CO_2 incubator. Cells were stimulated with 10 or 20 ng/mL of TNF-α (Peprotech, East Windsor, NJ, USA) to mimic the psoriatic model in vitro. Primary human keratinocytes (PHKs) were isolated from the foreskin of a healthy young male donor. All volunteers provided written informed consent. The study protocol was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB No. 2105-095-1219), and all experiments conformed to the principles of the Declaration of Helsinki. We obtained the informed consent from all participants or their legal guardians. PHKs were maintained in EpiLife medium supplemented with HKGS (Gibco) and antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin; WELGENE) at 37 °C in a humidified 5% CO_2 incubator.

Animal experiment

ICR mice (male, 12 weeks old) were purchased from OrientBio (OrientBio Inc., Seongnam, Korea). IL-22Rα knock-out (KO) mice were purchased from Jackson Laboratories (stock no. 031003, Strain: C57BL/6J; Jackson Laboratories, Sacramento, CA, USA). C57BL/6J mice maintained internal reproduction at the animal facility as wild-type (WT) mice. All mice were bred and housed under specific pathogen-free conditions at the animal facility of the Seoul National University College of Medicine. All mice were sacrificed by CO_2 inhalation to collect dorsal skin and ear tissue. Animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) of Seoul National University (approval no. SNU-220921-6-3). All experiments were conducted in accordance with the IACUC and ARRIVE guidelines.

IMQ-induced psoriasis-like mouse model

One day before psoriasis induction, the dorsal hair of the mice was shaved (day 0). IMQ (a topical dose of 83.3 mg Aldara cream (5% IMQ); 3 M Pharmaceuticals, Long Beach, CA, USA) was applied to the dorsal area and ear daily starting from day 1 up to day 7. Treatment group mice were administered either vehicle cream or alloferon cream every day after 6 h of IMQ application. After 7 days, the mice were sacrificed, and the dorsal skin and ear tissues were collected. Animal experiments were performed in three independent experiments.

Immunofluorescence (IF) analysis

HaCaT and PHK cells (4×10^4 cells/well) were seeded on 12-mm coverslips in a 24-well plate and stabilized overnight. Cells were washed with PBS and then treated with TNF-α (20 ng/mL) diluted in serum-free media for 24 h at 37 °C in a humidified 5% CO_2 incubator. After incubation, the media was aspirated, and alloferon (2 and 4 µg/mL) and diluted serum-free RPMI 1640 or EpiLife medium were added, and the mixture was incubated for another 24 h. After incubation, cells were washed twice with PBS and fixed with 4% paraformaldehyde (PFA) at 4°C for 15 min. Cells were washed twice with 0.5% bovine serum albumin (BSA) in PBS for 5 min each time and permeabilized with 0.3% Triton X-100 in PBS for 15 min at room temperature (RT). After washing with washing buffer (0.5% BSA, 0.3% Triton X-100 in PBS), cells were incubated with blocking buffer (0.5% BSA, 0.3% Triton X-100, 5% normal goat serum in PBS) for 1 h at RT. Cells were incubated with rabbit-developed anti-human IL-22Rα (1:150; Abcam, Cambridge, UK) and diluted with blocking buffer for 2 h at RT. After washing cells with washing buffer three times and incubation with a goat-developed anti-rabbit IgG conjugated with Alexa Fluor 488 (1:1,500, Invitrogen, Carlsbad, CA, USA) as a secondary antibody, cells were diluted with blocking buffer for 30 min at RT. After washing with washing buffer three times, cells were mounted with mounting medium and counterstained with 4′,6-diamidino-2-phenylindole (DAPI; ImmunoBioscience, Mukilteo, WA, USA). Signals were visualized using fluorescence microscopy (EVOS M5000, Invitrogen). Celleste 5 software (Invitrogen) was used to measure the fluorescent intensity.

Histological analysis

Dorsal skin and ear tissues were fixed in 4% PFA at 4 °C overnight. Tissues were then dehydrated and embedded in paraffin. Embedded tissues were sectioned into 4-µm thicknesses. After deparaffinization and hydration, the sections were stained with hematoxylin and eosin. Tissue sections were mounted (Sigma, St. Louis, MO, USA), and images were acquired using a microscope (EVOS M5000, Invitrogen). Epidermal thickness was measured in three parts per image using Celleste 5 software (Invitrogen).

Immunohistochemistry (IHC)

Dorsal skin tissue samples were fixed in 4% PFA at 4 °C overnight. Tissues were dehydrated and embedded in paraffin. Embedded tissues were sectioned into 4-µm thicknesses. After deparaffinization and hydration, an antigen epitope was retrieved by microwave heating with citrated buffer (pH 6.0). Endogenous peroxidase was blocked by treatment with 0.3% H_2O_2. The sections were blocked with 5% goat serum in PBS for 1 h at RT, and the sections were incubated with rabbit-developed anti-mouse IL-22Rα antibody (1:250, Millipore, St. Louis, MO, USA) overnight at 4 °C in the humid chamber. After incubation, the sections were incubated with biotinylated goat-developed anti-rabbit IgG for 1 h at RT, and then Avidin–Biotin Complex (ABC) solution

(Vector Laboratories, Burlingame, CA, USA) was applied to the sections for 40 min at RT. A DAB kit (Vector Laboratories) was used for chromogenic detection. Hematoxylin was then used for counterstaining. After dehydration and clearing, the sections were mounted using a mounting medium (Sigma). Images were acquired using a microscope (EVOS M5000, Invitrogen).

Microarray analysis

Gene expression by IL-22Rα KO mice treated with IMQ and alloferon was analyzed using Affymetrix GeneChip® Mouse Gene 2.0 ST arrays. The array chip has more than 33,000 probe sets at the gene level. Total mRNA was extracted from the dorsal skin using TRIzol (Invitrogen). One hundred nanograms of each RNA sample was subjected to the Affymetrix analytical procedure, as recommended by the manufacturer. The data were summarized and normalized using a robust multiaverage (RMA) method implemented in the Affymetrix® Power Tool. Gene enrichment and functional annotation analysis for a significant probe list was performed using Gene Ontology. All data analysis and visualization of differentially expressed genes were performed using R 3.3.2.

Statistical analysis

Experimental data were presented as mean ± standard deviation (SD). Comparisons between three or more groups were performed using one-way ANOVA. P values of 0.05 were used to indicate a statistically significant difference. Statistical analysis was performed using GraphPad InStat version 8.0.2 (GraphPad Software, La Jolla, CA, USA).

Data availability

The dataset (GSE285640) underlying this article is currently under embargo and will remain restricted until December 29, 2028. During this period, access can be obtained upon request to Y.K. The data will become accessible in a repository once the embargo period expires.

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References

1. Michalek, I. M., Loring, B. & John, S. M. A systematic review of worldwide epidemiology of psoriasis. *J. Eur. Acad. Dermatol. Venereol.* **31**, 205–212 (2017).
2. Damiani, G. et al. The global, regional, and National burden of psoriasis: results and insights from the global burden of disease 2019 study. *Front. Med.* **8**, 743180 (2021).
3. Iskandar, I., Parisi, R., Griffiths, C., Ashcroft, D. & Atlas, G. P. Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender. *Br. J. Dermatol.* **184**, 243–258 (2021).
4. Baliwag, J., Barnes, D. H. & Johnston, A. Cytokines in psoriasis. *Cytokine* **73**, 342–350 (2015).
5. Itoh, T. et al. Biological effects of IL-26 on T cell–mediated skin inflammation, including psoriasis. *J. Invest. Dermatol.* **139**, 878–889 (2019).
6. de Alcantara, C. C., Reiche, E. M. V. & Simão, A. N. C. Cytokines in psoriasis. *Adv. Clin. Chem.* **100**, 171–204 (2021).
7. Wu, S. et al. The potential of diosgenin in treating psoriasis: studies from HaCaT keratinocytes and imiquimod-induced murine model. *Life Sci.* **241**, 117115 (2020).
8. Reid, C. & Griffiths, E. M. Psoriasis and treatment: past, present and future aspects. *Acta Derm. Venereol.* **100**, 69–79 (2020).
9. Lee, H. J. & Kim, M. Challenges and future trends in the treatment of psoriasis. *Int. J. Mol. Sci.* **24**, 13313 (2023).
10. Hamilton, M. et al. Psoriasis treatment and management—a systematic review of full economic evaluations. *Br. J. Dermatol.* **172**, 574–583 (2015).
11. Mustonen, A., Mattila, K., Leino, M., Koulu, L. & Tuominen, R. The costs of psoriasis medications. *Dermatol. Ther.* **3**, 169–177 (2013).
12. Raho, G., Mihajlova Koleva, D., Garattini, L. & Naldi, L. The burden of moderate to severe psoriasis: an overview. *Pharmacoeconomics* **30**, 1005–1013 (2012).
13. Zhang, X., Retyunskiy, V., Qiao, S., Zhao, Y. & Tzeng, C. M. Alloferon-1 ameliorates acute inflammatory responses in λ-carrageenan-induced paw edema in mice. *Sci. Rep.* **12**, 16689 (2022).
14. Jo, H. et al. Alloferon affects the chemosensitivity of pancreatic Cancer by regulating the expression of SLC6A14. *Biomedicines* **10**, 896 (2022).
15. Chernysh, S. et al. Antiviral and antitumor peptides from insects. *Proc. Natl. Acad. Sci.* **99**, 12628–12632 (2002).
16. Kim, Y. et al. The anti-inflammatory effect of alloferon on UVB-induced skin inflammation through the down-regulation of pro-inflammatory cytokines. *Immunol. Lett.* **149**, 110–118 (2013).
17. Andoh, A. et al. Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. *Gastroenterology* **129**, 969–984 (2005).
18. Trivella, D. B. B., Ferreira-Júnior, J. R., Dumoutier, L., Renauld, J. C. & Polikarpov, I. Structure and function of interleukin-22 and other members of the interleukin-10 family. *Cell. Mol. Life Sci.* **67**, 2909–2935 (2010).
19. Aggarwal, S., Xie, M. H., Maruoka, M., Foster, J. & Gurney, A. L. Acinar cells of the pancreas are a target of interleukin-22. *J. Interferon Cytokine Res.* **21**, 1047–1053 (2001).
20. Dumoutier, L., Van Roost, E., Colau, D. & Renauld, J. C. Human interleukin-10-related T cell-derived inducible factor: molecular cloning and functional characterization as an hepatocyte-stimulating factor. *Proc. Natl. Acad. Sci.* **97**, 10144–10149 (2000).
21. Lejeune, D. et al. Interleukin-22 (IL-22) activates the JAK/STAT, ERK, JNK, and p38 MAP kinase pathways in a rat hepatoma cell line: pathways that are shared with and distinct from IL-10. *J. Biol. Chem.* **277**, 33676–33682 (2002).
22. Radaeva, S., Sun, R., Pan, H., Hong, F. & Gao, B. Interleukin 22 (IL-22) plays a protective role in T cell-mediated murine hepatitis: IL-22 is a survival factor for hepatocytes via STAT3 activation. *Hepatology* **39**, 1332–1342 (2004).
23. Fujita, H. The role of IL-22 and Th22 cells in human skin diseases. *J. Dermatol. Sci.* **72**, 3–8 (2013).
24. Yadav, D. & Sarvetnick, N. Cytokines and autoimmunity: redundancy defines their complex nature. *Curr. Opin. Immunol.* **15**, 697–703 (2003).
25. Prignano, F. & Donetti, E. Looking at Interleukin-22 from a new dermatological perspective: from epidermal homeostasis to its role in chronic skin diseases. *Dermatology* **238**, 829–836 (2022).
26. Mitra, A., Raychaudhuri, S. K. & Raychaudhuri, S. P. Functional role of IL-22 in psoriatic arthritis. *Arthritis Res. Ther.* **14**, 1–10 (2012).

27. Abdallah, F. et al. miR-21-3p/IL-22 axes are major drivers of psoriasis pathogenesis by modulating keratinocytes proliferation-survival balance and inflammatory response. *Cells* **10**, 2547 (2021).
28. Boniface, K. et al. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J. Immunol.* **174**, 3695–3702 (2005).
29. Boniface, K. et al. A role for T cell-derived Interleukin 22 in psoriatic skin inflammation. *Clin. Exp. Immunol.* **150**, 407–415 (2007).
30. Puigdevall, L., Michiels, C., Stewardson, C. & Dumoutier, L. JAK/STAT: why choose a classical or an alternative pathway when you can have both? *J. Cell. Mol. Med.* **26**, 1865–1875 (2022).
31. Kotenko, S. V. et al. Identification of the functional interleukin-22 (IL-22) receptor complex: the IL-10R2 chain (IL-10Rβ) is a common chain of both the IL-10 and IL-22 (IL-10-related T cell-derived inducible factor, IL-TIF) receptor complexes. *J. Biol. Chem.* **276**, 2725–2732 (2001).
32. Wu, Y. et al. Interleukin 22 in liver injury, inflammation and cancer. *Int. J. Biol. Sci.* **16**, 2405 (2020).
33. Yamanaka, K., Yamamoto, O. & Honda, T. Pathophysiology of psoriasis: a review. *J. Dermatol.* **48**, 722–731 (2021).
34. Flemming, J. P., Wermuth, P. J. & Mahoney, M. G. Extracellular vesicles in the skin microenvironment: emerging roles as biomarkers and therapeutic tools in dermatologic health and disease. *J. Invest. Dermatol.* (2023).
35. Tang, Z. L. et al. LncRNA MEG3 suppresses PI3K/AKT/mTOR signalling pathway to enhance autophagy and inhibit inflammation in TNF-α-treated keratinocytes and psoriatic mice. *Cytokine* **148**, 155657 (2021).
36. Choi, D. H. & Hwang, H. S. Anti-inflammation activity of Brazilin in TNF-α induced human psoriasis dermatitis skin model. *Appl. Biol. Chem.* **62**, 1–9 (2019).
37. Yanli, M., Yu, W. & Yuzhen, L. Elevated SIRT3 Parkin-dependently activates cell mitophagy to ameliorate TNF-α-induced psoriasis-related phenotypes in HaCaT cells through deacetylating FOXO3a for its activation. *Arch. Dermatol. Res.* **315**, 847–857 (2023).
38. Ma, H. L. et al. IL-22 is required for Th17 cell–mediated pathology in a mouse model of psoriasis-like skin inflammation. *J. Clin. Invest.* **118**, 597–607 (2008).
39. Seth, P. & Dubey, S. IL-22 as a target for therapeutic intervention: current knowledge on its role in various diseases. *Cytokine* **169**, 156293 (2023).
40. Sonnenberg, G. F., Fouser, L. A. & Artis, D. Functional biology of the IL-22-IL-22R pathway in regulating immunity and inflammation at barrier surfaces. *Adv. Immunol.* **107**, 1–29 (2010).
41. Bae, S. et al. The effect of alloferon on the enhancement of NK cell cytotoxicity against cancer via the up-regulation of Perforin/granzyme B secretion. *Immunobiology* **218**, 1026–1033 (2013).
42. Jeon, J., Kim, Y., Kim, H., Kang, J. S. & Lee, W. J. Anti-inflammatory effect of alloferon on ovalbumin-induced asthma. *Immune Netw.* **15**, 304–312 (2015).
43. Jo, H., Kim, Y., Shin, S. & Kang, J. S. Abstract C123: alloferon inhibits migration of pancreatic cancer by regulating the expression of IL-22Rα. *Mol. Cancer Ther.* **22**, C123–C123 (2023).
44. Kim, Y. et al. The pathogenic role of interleukin-22 and its receptor during UVB-induced skin inflammation. *PLoS One* **12**, e0178567 (2017).
45. Hawkes, J. E., Yan, B. Y., Chan, T. C. & Krueger, J. G. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J. Immunol.* **201**, 1605–1613 (2018).
46. Oral, H. B. et al. Regulation of T cells and cytokines by the interleukin-10 (IL-10)-family cytokines IL-19, IL-20, IL-22, IL-24 andIL-26. *Eur. J. Immunol.* **36**, 380–388 (2006).
47. Blumberg, H. et al. Interleukin 20: discovery, receptor identification, and role in epidermal function. *Cell* **104**, 9–19 (2001).
48. Alunno, A. et al. Targeting the IL-23/IL-17 axis for the treatment of psoriasis and psoriatic arthritis. *Expert Opin. Biol. Ther.* **15**, 1727–1737 (2015).
49. Boutet, M. A., Nerviani, A., Gallo Afflitto, G. & Pitzalis, C. Role of the IL-23/IL-17 axis in psoriasis and psoriatic arthritis: the clinical importance of its divergence in skin and joints. *Int. J. Mol. Sci.* **19**, 530 (2018).
50. Bruno, M. et al. Immunological effects of Anti–IL-17/12/23 therapy in patients with psoriasis complicated by Candida infections. *J. Invest. Dermatol.* **142**, 2929–2939 (2022). e2928.
51. Steiniche, T. et al. Epidermal overexpression of interleukin-19 and-20 mRNA in psoriatic skin disappears after short-term treatment with cyclosporine a or calcipotriol. *J. Invest. Dermatol.* **121**, 1306–1311 (2003).
52. Witte, E. et al. IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis. *J. Invest. Dermatol.* **134**, 2757–2767 (2014).
53. Garber, K. Psoriasis: from bed to bench and back: advances in immunology, a focus on human tissue and a Dash of luck have given dermatologists several highly effective psoriasis therapies, of which stelara is the latest. *Nat. Biotechnol.* **29**, 563–567 (2011).
54. Travis, S. Vol. 14 1–3 (Oxford University Press, 2020).
55. Hendrix, N. et al. Cost-effectiveness of targeted pharmacotherapy for moderate to severe plaque psoriasis. *J. Manag Care Spec. Pharm.* **24**, 1210–1217 (2018).

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Author contributions

Conceptualization: JSK and YK; Data Curation: YK, TA, and HJ; Funding Acquisition: YK; Investigation: YK, TA, HJ, ISG, CWC, YJ, and SS; Project Administration: JSK and YK; Visualization: TA and HJ; Writing-Original Draft Preparation: JSK and YK. All authors reviewed the manuscript.

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Competing interests

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Additional information

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Correspondence and requests for materials should be addressed to J.S.K. or Y.K.