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Full-length Article

From skin to spinal Cord: How IL-17a Drives psoriatic chronic itch

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ABSTRACT

Interleukin-17a (IL-17a) has been established as a master regulator of inflammatory cascades in psoriasis pathogenesis. Monoclonal antibodies targeting IL-17a have demonstrated significant efficacy in relieving psoriasis-related symptoms, including the rapid alleviation of chronic itching. However, whether IL-17a is involved in chronic psoriatic pruritus and the specific mechanisms of its action remain poorly understood. In this study, we demonstrate that IL-17a significantly exacerbates chronic itch in a murine model of psoriasis. Mechanistically, IL-17a upregulation in psoriatic skin tissues activated the IL-17a receptor (IL-17Ra) in sensory neurons, subsequently promoting the expression of IL-6 in dorsal root ganglion (DRG) neurons. This neuron-derived IL-6 is transported via sensory nerve fibers to the spinal dorsal horn (SDH), where it triggers astrocyte activation and subsequent IL-1β secretion to potentiates chronic itch signaling in psoriasis. Our findings uncover a neuroimmune circuit in which IL-17a-IL-17Ra signaling on sensory neurons mediates the propagation of pruritic signals from peripheral skin to the central nervous system, with spinal IL-6-astrocyte-IL-1β axis serving as an amplifier of psoriatic pruritus.

1. Introduction

Psoriasis is a chronic immune-mediated disorder characterized by immune cell infiltration, epidermal hyper-proliferation, and abnormal keratinocyte differentiation. The pathogenesis of psoriasis is multifaceted and the interleukin (IL)–23/T helper 17(Th17) pathway is crucial. IL-17a serves as the chief effector in this pathway and orchestrates the advancement of inflammation by interacting with IL-17 receptors. The IL-17 receptor family encompasses five members: IL-17Ra, Rb, Rc, Rd, and Re, which couple to form a hetero-receptor complex (Chen et al., 2023; Cole et al., 2023).IL-17Ra is a common subunit of all hetero-receptors and is widely expressed in various skin tissues cell types, including keratinocytes, dendritic cells, and fibroblasts (Vidal et al., 2021). Specifically, IL-17a interacts with IL-17Ra in keratinocytes, thereby directly stimulating their proliferation and inducing the production of various chemokines, such as CXCL2. This process facilitates the recruitment of neutrophils to the epidermis and contributes to the formation of localized microabscesses (Moos et al., 2019). Furthermore, IL-17a affects fibroblasts and dendritic cells by increasing the expression of IL-6 and IL-23, which in turn promote the differentiation of T cells into the Th17 phenotype through IL-17Ra(Ma et al., 2023; Nakamizo et al., 2021). Recent research has indicated that the location of IL-17Ra on sensory neurons suggests their susceptibility to peripheral IL-17a stimulation, potentially facilitating the restoration of impaired sensory neurons, thereby influencing the skin wound healing process (Enamorado et al., 2023). This elucidates the pivotal function of IL-17Ra in sensory neurons in modulating skin wound healing, underscoring the potential regulatory impact of IL-17Ra located in sensory neurons on the

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pathophysiology of the skin system.

Reportedly, approximately 60 %–90 % of patients with psoriasis also suffer from chronic pruritus(Hawro et al., 2020; Kaczmarska et al., 2023). Sustained itching places a substantial burden on patients, resulting in a pronounced decline in their quality of life. However, the mechanism underlying pruritus in psoriasis remains unclear and effective treatment methods are still lacking (Komiya et al., 2020). Several studies have explored the involvement of IL-17a in nociception, where low-dose IL-17a was found to selectively trigger nociceptors and elicit mechanical pain specifically in female subjects (Luo et al., 2021; Sun et al., 2023). However, the potential role of IL-17a in the pathogenesis of pruritus remains unexplored.

Inflammatory cytokines, including IL-4 (Oetjen et al., 2017), IL-33 (Imai, 2019) and IL-31 (Datsi et al., 2021), have been identified as triggers of pruritus in chronic skin diseases, particularly in atopic dermatitis. Clinical studies have revealed that biological therapeutic methods targeting these cytokines can effectively alleviate chronic pruritus symptoms (Vander Does et al., 2023; Zhou et al., 2021), which further confirm the important role of these inflammatory factors in chronic pruritus. Additionally, IL-17a inhibitors have depicted promising efficacy in treating patients with psoriasis, with multiple studies indicating that anti-IL-17a therapy proved the most effective in reducing pruritus in psoriasis (Kimball et al., 2018; Reich et al., 2023; Thérénéet al., 2018). However, whether IL-17a is involved in psoriasis-associated chronic itching remains to be determined.

Here, we elucidated the mechanisms underlying IL-17a-mediated chronic pruritus in psoriatic pathology. Our findings established that IL-17Ra expressed on nociceptive neurons serves as a critical mediator of psoriatic itch transduction, with neuron-derived IL-6 emerging as the principal downstream effector in this signaling cascade. Through systematic experimentation, we demonstrate that psoriatic inflammation induces pathological IL-6 hypersecretion from dorsal root ganglion (DRG) neurons, which subsequently activate spinal cord astrocytes via a STAT3-dependent mechanism. This glial activation subsequently triggers IL-1β release, which exacerbates psoriasis-related chronic itch. Notably, genetic ablation of IL-17ra in sensory neurons and targeted IL-6 silencing via adeno-associated virus (AAV)-shRNA delivery attenuated both imiquimod (IMQ)-induced scratching and spinal astrogliosis in murine models. Furthermore, therapeutic application of an IL-17a monoclonal antibody effectively attenuated IMQ-induced scratching behaviors and reduced IL-1β release from spinal astrocytes. This investigation established the mechanistic pathway through which IL-17a exacerbates psoriatic pruritus, highlighting the critical role of sensory neuron IL-17Ra signaling and subsequent IL-6 secretion in mediating neuroimmune crosstalk.

2. Materials and methods

2.1. Animals

C57BL/6J mice were purchased from the Beijing Vital River Laboratory Animal Technology (Beijing). The IL-17Ra$^{flox+/+}$ and advillin-Cre mice were purchased from GemPharmatech Corporation (Nanjing). All procedures involving animal experimentation adhered to the Guide for the Care and Use of Laboratory Animals and relevant ethical regulations outlined by the National Institutes of Health Guidelines. This study was approved by the Experimental Animal Welfare and Ethics Review Committee of the Wuhan Youdu Biotechnology Co., Ltd. (Wuhan).

2.2. IMQ induced psoriatic mouse model and behavioral studies

Mice were allowed 30 min to acclimatize to their test environment over a period of 3 to 5 days. Psoriatic mouse models were induced by applying 5 % IMQ (Mingxin Pharmaceuticals, Sichuan to shaved neck skin (2 cm^2) for 5 consecutive days. Mice in the control group were treated with vaseline jelly. To conduct the spontaneous itching test, individual mice were placed in transparent boxes and their scratching behavior was recorded for 1 h using a camera, as previously described (Liu et al., 2022).

2.3. Western blotting

Protein was extracted from the segments from C5 to L1 of the mice spinal cord and the cultured C8-D1A astrocytes. This procedure was performed as described in our previous study (Liu et al., 2017). The primary antibodies used in this study were as follows: p-Stat3(1:1000, Cell signal technology), Stat3(1:1000, Cell signal technology), Beta-actin (1:10000, Proteintech), IL-6 (1:800, Affinity), IL-1β (1:800, Proteintech) and Lcn2 (1:800 abclonal). The secondary antibodies used were horseradish peroxidase-conjugated goat anti-rabbit IgG (1:20000, abclonal) and were horseradish peroxidase-conjugated goat anti-mouse IgG (1:20000, abclonal). The relative optical density was quantified using ImageJ software to calculate the relative expression levels of the proteins.

2.4. RNA Isolation and quantitative PCR

DRG tissue and cultured neural cells were homogenized in TRIzol reagent (Takara) to extract total RNA following the manufacturer's protocol. The isolated RNA was then reverse transcribed into cDNA using the PrimeScript™ RT reagent Kit (Takara). Real-time quantitative PCR was performed using the SYBR Green Master Mix (Vazyme Biotech). Gene expression levels were analyzed using the $2^{-\Delta\Delta CT}$ method. The Primers used are detailed in Table S1 and were sourced from Qingke Biotech Corporation (Beijing, China).

2.5. Histological assay

Skin tissue samples were fixed in 4 % paraformaldehyde, embedded in paraffin, and sectioned for hematoxylin and eosin (H&E) staining. Images were captured using a microscope (DP80, Olympus) at 200X magnification. The epidermal thickness was measured according to the H&E-stained images using ImageJ software.

2.6. Astrocyte cell culture

Mouse astrocytes (C8-D1A) were purchased from Procell Life Science and Technology Company (Wuhan)(Yang et al., 2024). The cells were cultured in DMEM (Gibco), supplemented with 10 % FBS (Gibco) and 1 % penicillin–streptomycin (Gibco), and incubated at 37 °C in a humidified atmosphere with 5 % CO_2. Cultured cells were treated with different concentration of IL-6 (MCE) in for 6 h, and cell culture supernatants and proteins were extracted for subsequent detection.

2.7. Primary DRG neuron cells culture

Primary DRG neurons were extracted as previously described (Enamorado et al., 2023). Briefly, DRGs were collected from young mice (4 weeks) and incubated with 1 mg/ml collagenase A (Sigma) and 2.5 mg/ml dispase II (Sigma) for 90 min at 37 °C. DMEM supplemented with 10 % FBS (Thermo Fisher Scientific) was added to the DRG suspension and mixed thoroughly to ensure homogenization. After centrifugation, the supernatant was removed and the cell pellet was resuspended in DMEM supplemented with 10 % FBS, layered on a 10 % Percoll gradient (Biosharp) and centrifuged at 260 g for 10 min. After removing the supernatant and debris, the neuronal cells were resuspended in neurobasal medium (Gibco). Next, 5000 cells were seeded onto poly-d-lysine (Sigma) coated plates (Corning). After 4 h, the medium was replaced with a neurobasal medium containing 50 ng/mL nerve growth factor (Gibco) and 2 % B27 (Thermo Fisher Scientifi).

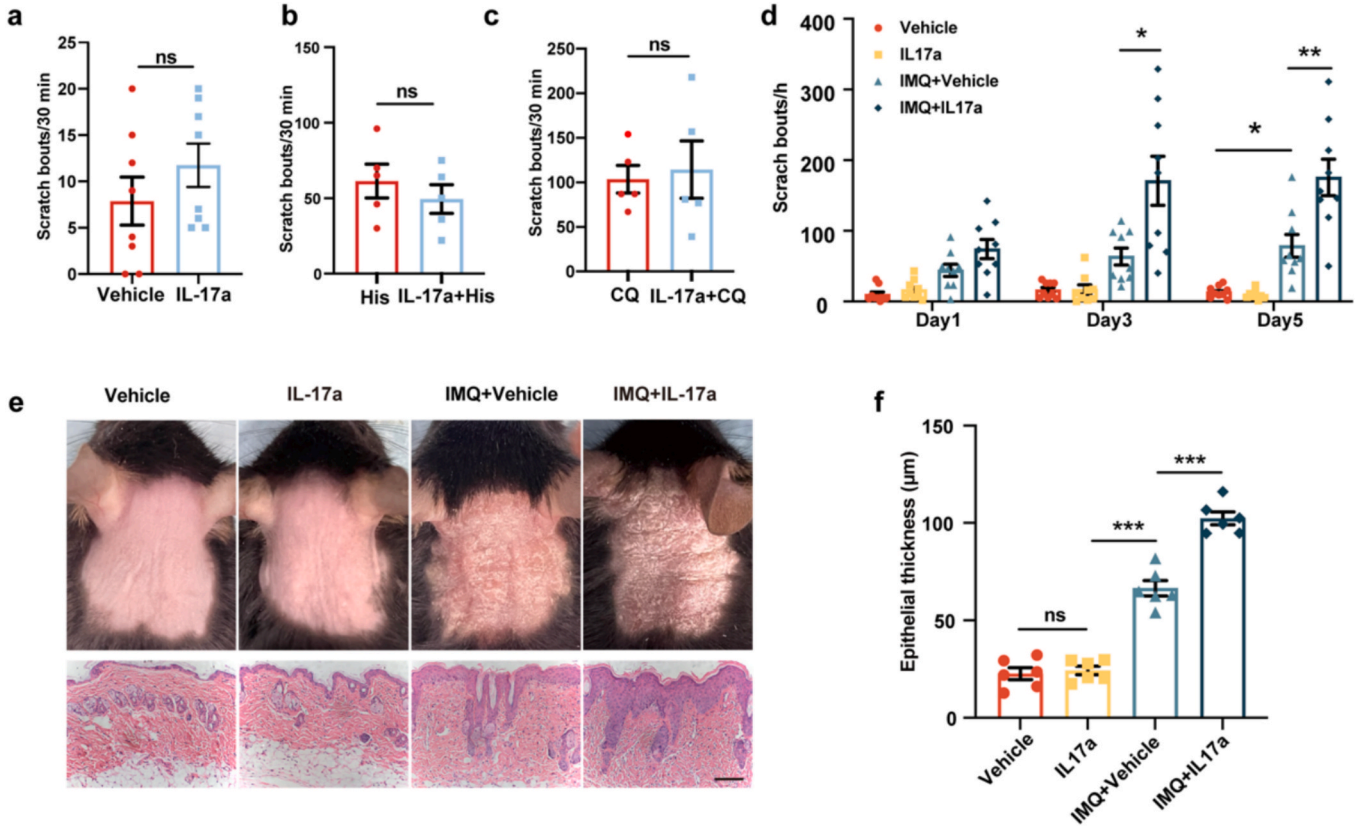

Fig. 1. IL-17a promote the chronic itch in IMQ- induced psoriasis. (a) Acute scratching was observed by subcutaneous injection of IL-17a (100 ng). (b) Acute scratching was observed by subcutaneous injection of histamine (200ug) and IL-17a (100 ng) or with (c) chloroquine (500ug) and IL-17a (100 ng). (d) Observe the effect of IL-17a on chronic scratching behavior induced by IMQ in mice. (e) Representative photograph of mouse back skin hematoxylin and eosin (HE) stained of mouse skin is shown below, Scale bar = 100 μm. (f) Epithelial thickness was measured according to the HE stains photos. Data are representative of three independent experiments and shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

2.8. DRG neurone cells / astrocytes co-culture

For co-culture studies, a Transwell 24-well plate (0.4 μm, Corning) was utilized. Neuronal cells were extracted using the aforementioned method and seeded onto a Transwell insert (5000 cells /insert). The DRG neuron cells were cultured alone for 5 days. Subsequently, astrocytes were added to the lower chamber for co-culture with anti-IL-6 (500 ng/ml, BioXcell) and pretreated in the astrocyte culture media for 2 h, followed by the addition of IL-17a (100 ng/ml, MCE) to the neuronal culture system. The astrocytes were collected after 12 h for subsequent analyses.

2.9. ELISA

Supernatants from cultured DRG neurons were collected to detect the IL-6 levels using a Mouse IL-6 ELISA kit (Service). The supernatant of the cultured astrocytes was used to detected the IL-1β level by using a Mouse IL-1β ELISA kit (Service). All procedures were performed according to the manufacturer's instructions.

2.10. Specific knockdown of IL-6 on DRG neuron using AAV vector encoding shRNA

Recombinant AAV (AAV-hSyn-EGFP-miR-shRNA-IL-6) vectors and control vectors were created by Braincase. A volume of 5 μL (1 × 10^13 viral genome copies/mL) virus was then injected into the tail vein of 4-week-old mice to specifically knock down IL-6 in DRG neurons as described previously(Shiratori-Hayashi et al., 2015). After 4 weeks, the mice were used for subsequent experiments. The IMQ-induced psoriasis model was established after 4 weeks after viral infusion.

2.11. Drugs administration

The intrathecal injection was performed by puncturing the spinal cord between L5 and L6 with a microinjector. 10 ul of the following agents were separately intrathecal injected into the spinal cord: LAA (L-α-aminoadipate, LAA) (100 nmol, Sigma), anti-IL-6 (50ug, BioXcell), anti-IL-1β (50ug, BioXcell), or an equivalent dose of an isotype control (50 μg; BioXcell). For intracutaneous administration, IL-17a (100 ng, MCE, USA), anti-IL-17a (10 mg/kg, BioXcell), and the corresponding isotype control (10 mg/kg, BioXcell) were injected.

2.12. Immunofluorescence

The DRG at the C3-T2 level and the spinal cord at the C3-C5 level were collected and fixed in 4 % paraformaldehyde. Subsequently, they were dehydrated in 30 % sucrose, embedded in OCT, anWEd sectioned into 15 μm slices. The sections were first blocked in 5 % donkey serum for 1 h at 37 °C. Next, they were incubated overnight at 4 °C with the following primary antibodies: anti-p-state3 (1:100, SANTA CRUZ), anti-GFAP (1:600, Proteintech), anti-IL-6 (1:200, RD system), and anti-IL-17Ra (1:200, Abcam). The sections were then incubated with Alexa Fluor 594- or Alexa Fluor 488-conjugated secondary antibodies for 1 h. Finally, the sections were stained with DAPI for the nucleus and mounted on coverslips. Fluorescent images were acquired using a confocal microscope.

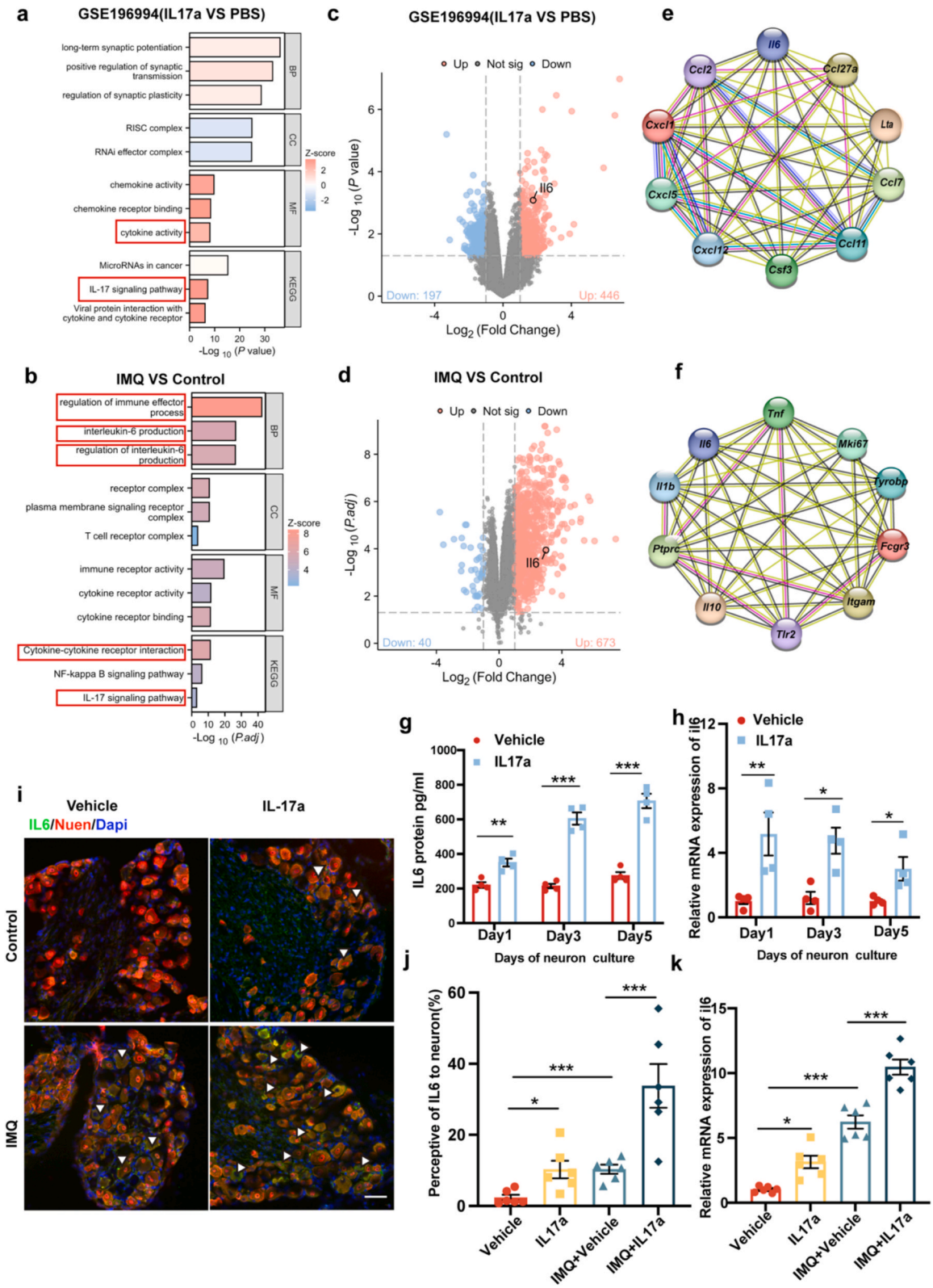

Fig. 2. IL-17a upregulated the expression of IL6 in DRG neurons. (a) Go and KEGG analyze of the differentially expressed genes (DEG) in the GSE196994 database. (b) Go and KEGG analyze of the DEG in the mouse DRG tissue. (c)Volcano plot of DEG in the GSE196994database. (d) Volcano plot of DEG in mouse DRG tissue. (e) The 10-hub gene was analysis by cytoscape software according to the DEG in (c). (f) The 10-hub gene was analysis by cytoscape software according to the DEG in (d). (g) The IL-6 protein level was measured by ELISA. (h) The IL-6 mRNA level was measured by q-PCR. (i, j) The IL-6 expression in DRG neurons was detected by immunofluorescent staining. Scale bar = 100 μm. (k) The mRNA level of IL-6 in DRG neurons was detected by q-PCR. Data are representative of three independent experiments and shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

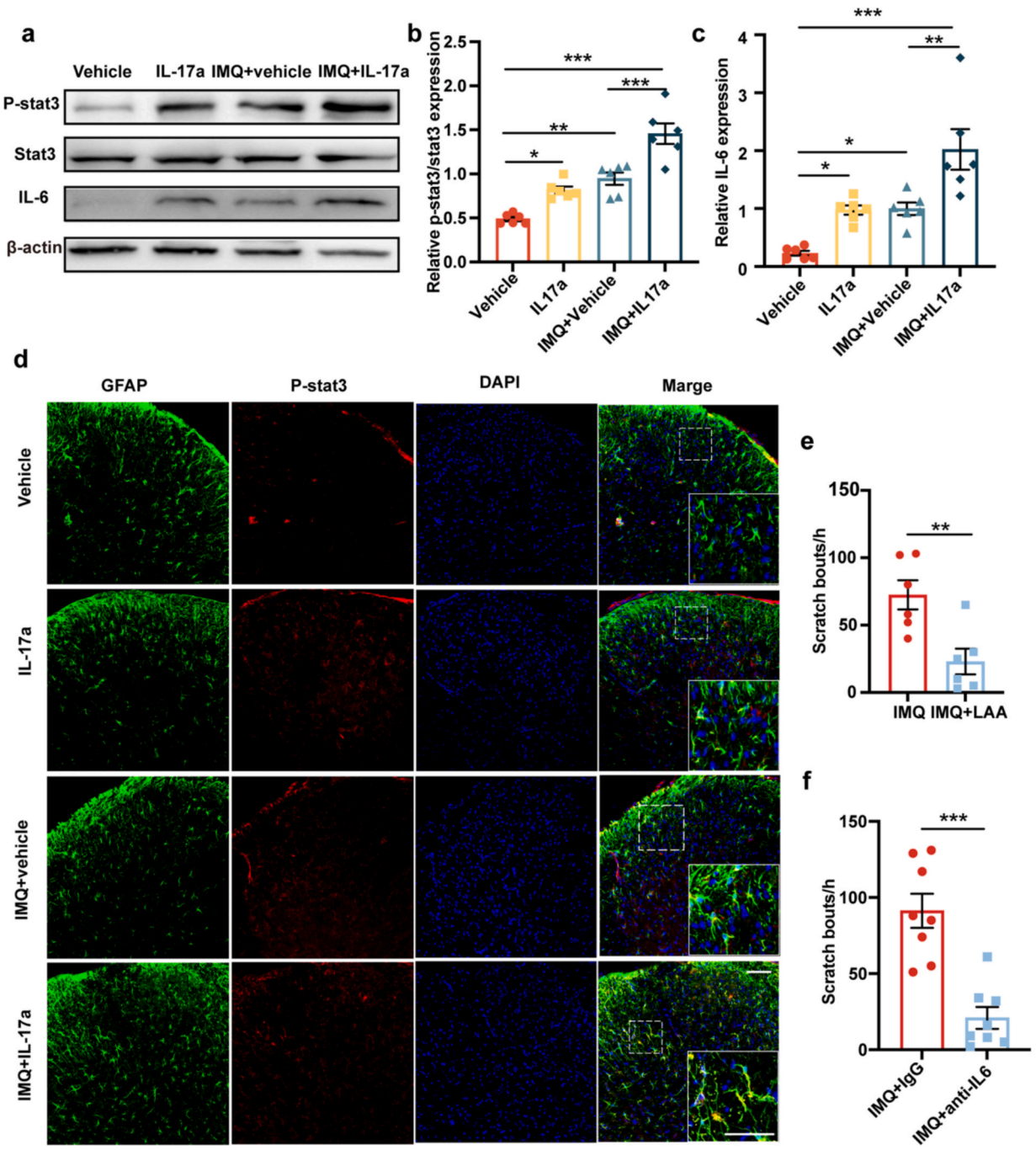

Fig. 3. IL6 promote the activation and proliferation of astrocyte in SDH. (a, b, c) Western blotting detected the IL-6, p-Stat3, state3 level in spinal cord. (d) Co-immunofluorescence used to detect the phosphorylation of stats in astrocyte on the SDH, scale bare = 100 μm. (e) Chronic scratch behavior was detected on day5 of IMQ-induced psoriatic mice treated with LAA. (f) Chronic scratch behavior was detected on day 5 of IMQ-induced psoriatic mice treated with anti-IL-6. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

2.13. Rna-sequence Data analysis

The RNA sequence data of the sensory neurons were downloaded from the National Institutes of Health's Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo) under the accession number GSE196994. Mouse DRG tissue was collected and sent to Shenzhen Huada Gene Company (Shenzhen, China) for transcriptome sequencing utilizing the BGISEQ platform. DESeq2 was used to analyze the differential expression between the two groups. The corrected P-value and | log2foldchange| were used as the threshold for significantly difference expression. Corrected P value ≤ 5 %, and $|\log_2$ Fold Change$| \geq 1$ were identified as the criteria for the declaration of significant differentially expressed genes (DEGs). Data were available from the NCBI GEO database (GSE276367).

2.14. Statistical Analyses

Statistical analyses were conducted using GraphPad Prism 8 software. Data were presented as means ± standard error of mean (SEM). Group means were compared using the two-tailed *t* test and analyzed across groups using one- and two-way analyses of variance. Significance levels were set at *p < 0.05, **p < 0.01, ***p < 0.001, with 'ns'

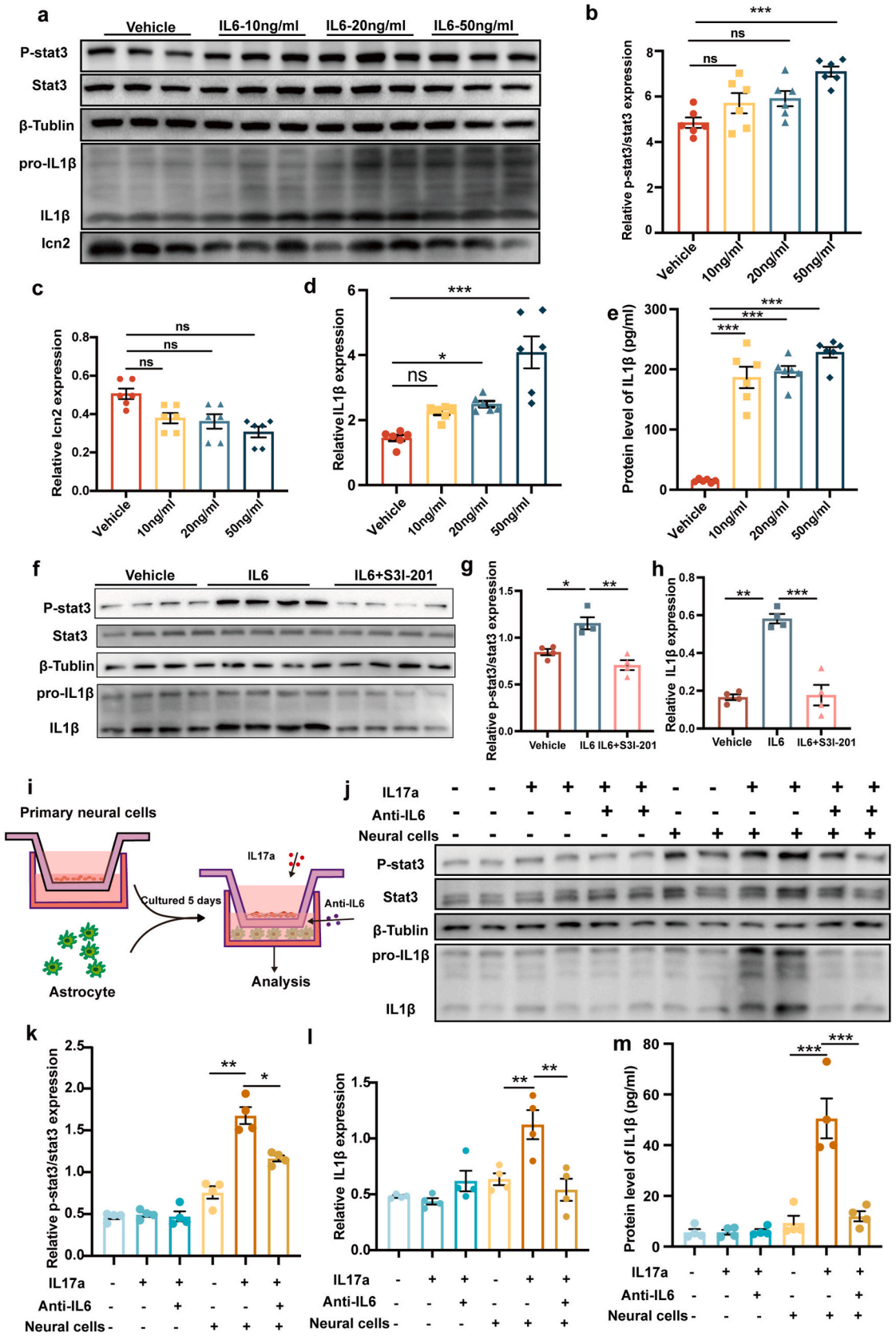

Fig. 4. IL-6 promoted the release of IL-1β by activating astrocytes in SDH. (a, b, c, d) Western blotting detecting the protein level of Stat3, P-Stat3, IL1β, IL6 and Lcn2 in the culture astrocyte. (e) The level of IL1β in supernatant of culture astrocyte was detected by ELISA. (f) Flow chart of the co-culture of DRG neuron cells and the astrocytes. (f, g,h) Western blotting detected the protein level of p-Stat3, Stat3, IL1β in the cultured astrocyte. (j, k, l) Western blotting detected the protein level of Stat3,P-Stat3 and IL1β in the cultured astrocyte. (m) The level of IL1β in supernatant of co-culture astrocyte was detected by ELISA. Data are representative of three independent experiments and shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

indicating non-significance.

3. Results

3.1. IL-17a promoted the chronic itch in psoriasis

To determine the pruritogenic potential of IL-17a, we intracutaneously injected 100 ng of IL-17a into the dorsal skin of mice and monitored scratching behavior within 30 min post-injection. Administration of IL-17a failed to elicit significant scratching episodes compared to that with vehicle controls (Fig. 1a), suggesting that IL-17a alone does not function as a direct pruritogen. Furthermore, we investigated whether IL-17a could potentiate the itching response triggered by other pruritogens, including histamine and chloroquine. However, intracutaneous injection of IL-17a at the same dose did not aggravate the acute itching response caused by these pruritogens (Figs. 1b, c).

IL-17a is identified as a crucial pathogenic element in psoriasis and in IMQ-induced psoriasis-like dermatitis (van der Fits et al., 2009). Accordingly, we explored the potential role of IL-17a in the development of chronic pruritus in psoriasis through intracutaneous administration of a consistent dose of IL-17a to mice with IMQ-induced psoriasis-like symptoms. Unexpectedly, IL-17a markedly exacerbated chronic pruritus in IMQ-treated mice, although the same dose of IL-17a did not induce pruritic behavior in control mice (Fig. 1d). Histopathological examination illustrated that the a low-dose of IL-17a alone did not cause significant pathological changes in the mouse skin. Nevertheless, low-dose IL-17a intensified IMQ-induced pathological alterations in mice, potentially due to the exacerbation of lesion progression through scratching behaviors (Figs. 1e, f). These findings show that IL-17a specifically plays a contributory role in chronic pruritus in psoriasis.

3.2. IL-17a upregulated the IL-6 expression in DRG neurons

IL-17a released from Th17 cells in the skin can signal to IL-17Ra in sensory neurons, subsequently modulating neuronal transcription processes (Enamorado et al., 2023). Thus, we postulated that IL-17a in psoriatic skin tissues could send direct signals to sensory neurons, thereby exacerbating pruritic behavior. To elucidate the potential mechanism by which IL-17a exacerbates pruritus in psoriasis, we reanalyzed the RNA sequencing (RNA-seq) data from *in vitro* IL-17a-treated DRG neuronal cells (GSE196994) (Enamorado et al., 2023). Through the GO and KEGG enrichment analyses of the differentially expressed genes (DEGs), we found that the IL-17a stimulation upregulated cytokine activity pathway and IL-17 signaling pathways (Fig. 2a) in cultured DRG neuronal cells. Furthermore, we extracted the DRG tissue from the psoriatic mouse model and control mice for RAN-seq. GO and KEGG analyses of the DEGs also showed that the IL-17 signaling pathway and the cytokine receptor activity pathway were enrichment. In particular, IL-6 production and regulation of IL-6 production pathway were significantly enriched in the DRG tissues of IMQ-treated mice (Fig. 2b). We found that the *IL6* was up-regulated in the GSE196994 database (Fig. 2c) and in the DRG tissues of IMQ-treated mice (Fig. 2d). To identify key regulatory molecules, STRING and Cytoscape with the CytoHubba plugin were used to identify the top 10 hub genes among all DEGs in the GSE196994 database, which showed that *IL6* had the highest node scores (Fig. 2e and Table S2). Notably, *IL6* also maintained its position within the top 10 hub genes in the DEGs from the IMQ-treated DRG tissues (Fig. 2f and Table S3). All evidence indicates that IL-17a stimulation may exert a considerable influence on the expression of IL-6 in neuronal cells. Reportedly, the upregulation of IL-6 expression in DRG tissues contributes to the exacerbation of chronic pruritus in contact dermatitis (Shiratori-Hayashi et al., 2021). Consequently, we hypothesized that IL-17a exacerbates chronic itching in psoriasis, which may be associated with the upregulation of IL-6 expression in DRG tissues.

To verify the effect of IL-17a on IL-6 expression in DRG neuron cells, we isolated DRG neuron cells and exposed them to IL-17a *in vitro*. It was observed that IL-17a markedly enhanced *IL-6* mRNA levels and extracellular IL-6 protein secretion in the DRG neurons (Figs. 2g, h). Subsequently, the *in vivo* expression of IL-6 was confirmed by detecting IL-6 expression in the DRG tissue of mice. Notably, IL-6 expression was substantially elevated in DRG tissues following intracutaneous injection of IL-17a and application of IMQ. Additionally, intracutaneous injection of IL-17a in IMQ-induced psoriasis model mice further promoted IL-6 expression in DRG tissues (Figs. 2i, j, k). These results indicate that the upregulation of IL-17a in psoriatic skin tissues promotes IL-6 expression in DRG tissues, which may in turn exacerbate chronic itching in psoriasis.

3.3. Elevated IL-6 in DRG tissue Aggravated psoriatic chronic itch

Reportedly, elevated levels of IL-6 in DRG tissue can be transported to the spinal dorsal horn (SDH), leading to the activation of the Stat3 pathway in astrocytes within the SDH, thereby potentially exacerbating the chronic itching associated with contact dermatitis(Shiratori-Hayashi et al., 2021). Additionally, Stat3-dependent reactive astrocytes are vital for amplifying chronic itching in mouse models of atopic dermatitis and contact dermatitis(Du et al., 2025; Shiratori-Hayashi et al., 2015). Consequently, we investigated whether IL-6 upregulation in the DRG tissues of IMQ-induced psoriatic mice could drive astrocytic Stat3 activation in the spinal cord to exacerbate psoriatic itching. Results indicated that both IL-17a administration and IMQ treatment led to a notable increase in IL-6 expression in the spinal cord (Figs. 3a, b). This upregulation of IL-6 expression in the spinal cord markedly promoted astrogliosis and phosphorylation of the Stat3 (P-Stat3) in astrocytes within the SDH. This effect was observed in mice that received intracutaneous injections of IL-17a and in mice with IMQ-induced psoriasis. Furthermore, this phenomenon was more pronounced in mice with IMQ-induced psoriasis following intracutaneous injection of IL-17a (Figs. 3c, d).

To determine the role of SDH astrocytes in psoriatic itch, we intrathecally administered the astrocyte-specific inhibitor LAA. (Fig. S1a). Astrocytic suppression significantly attenuated chronic scratching behaviors and improved cutaneous pathology in mice with psoriasis (Fig. 3e; S1b, c), without affecting the acute itch responses to chloroquine or histamine (Fig. S1d, e). Next, we analyzed the role of IL-6 in DRG tissue in chronic itching of psoriatic mice through intrathecal administration of an anti-IL-6. We found that the anti-IL-6 therapy also resulted in a significant decrease in scratching behavior in mice with psoriasis and a noticeable improvement in the skin lesions induced by IMQ (Fig. 3f; S1f, g). Inhibition of IL-6 signaling in the spinal cord significantly reduced IMQ-induced astrocyte proliferation in the SDH (Fig. S1h, i). Importantly, IL-6 neutralization did not inhibit acute scratching behavior caused by chloroquine or histamine (Fig. S1j, k). These findings suggest that elevated levels of IL-6 in DRG tissue may activate the Stat3 pathway in spinal cord astrocytes, thereby modulating chronic itch associated with psoriasis, without affecting the transmission of acute itch.

3.4. IL-6 promoted the release of IL-1β by activating astrocytes in SDH

To investigate the potential mechanism by which IL-6 activates astrocytes to promote chronic itching in psoriasis, we stimulated mouse C8-D1A astrocytes with IL-6 at three different concentrations. We found that each concentration of IL-6 significantly increased Stat3 phosphorylation in astrocytes (Figs. 4a, b). Lipocalin-2 (Lcn2) has been identified as a pruritogenic mediator secreted by reactive astrocytes (Du et al., 2025; Shiratori-Hayashi et al., 2015). However, our data indicated that IL-6 did not directly enhance Lcn2 expression in astrocytes (Figs. 4a, c). Intriguingly, IL-6 stimulation triggered substantial IL-1β secretion from astrocytes in a dose-dependent manner (Figs. 4a, d, e). IL-1β within the spinal cord has been implicated in the potentiation of gastrin-releasing

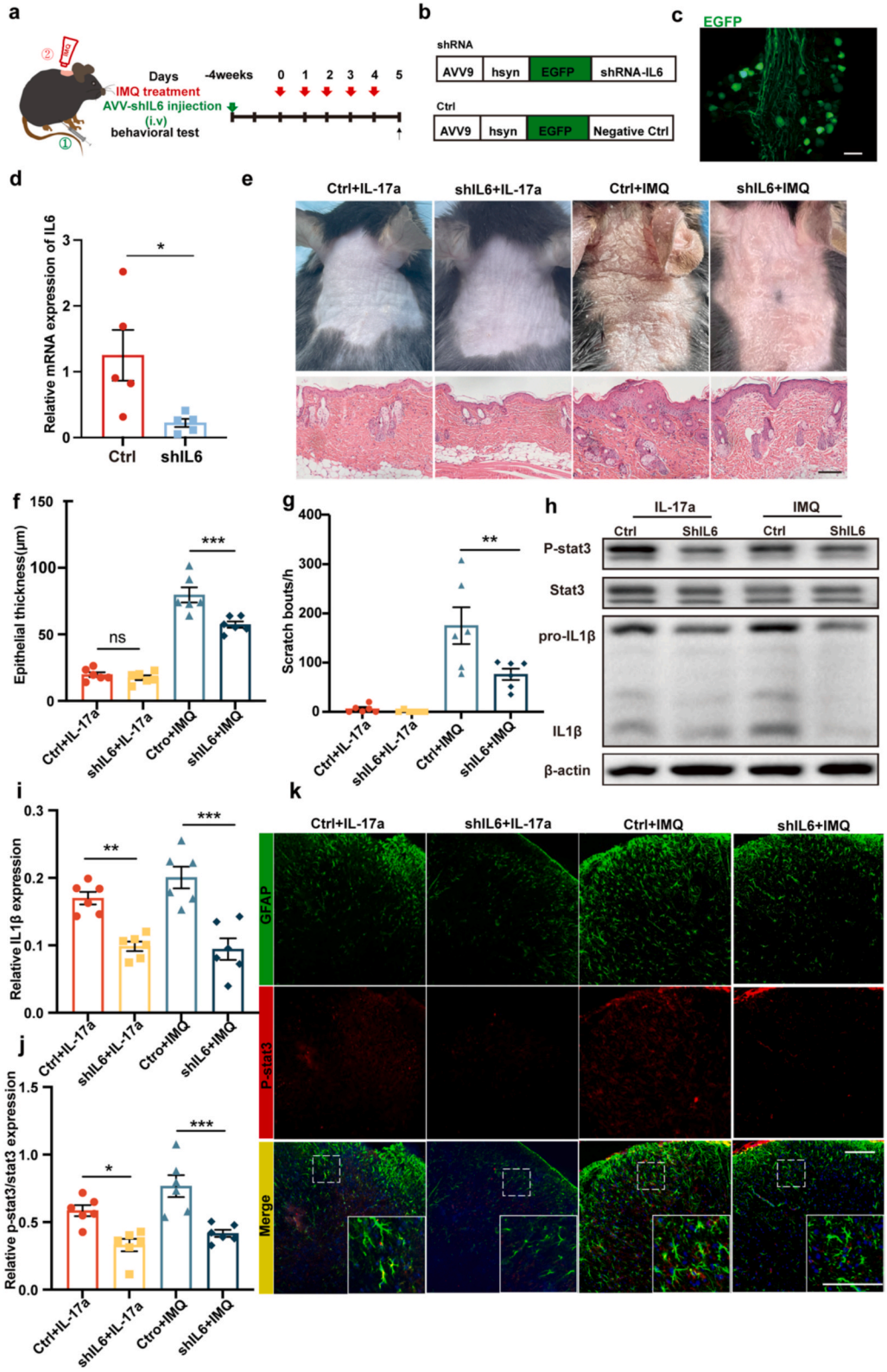

Fig. 5. IL-6 Knockdown in DRG neurons attenuated psoriasis-associated chronic itching (a) Flow chart of the application of AVV-shIL6 in IMQ-induce psoriatic mice. (b) Schematics of control and sh-IL6 AAV constructs. (c) The GFP signal was detected by IF in the DRG tissue, Scale bar = 100 um. (d) q-PCR was used to detected the mRNA of IL6 in the DRG tissue. (e) Photograph of mouse back skin and HE stained of mouse skin is shown below. Scale bar = 100 um. (f) Epithelial thickness was measured according to the HE stains photos. (g) Chronic scratch behavior was detected on day5 of IMQ administration. (h, i, j) Western blotting detected the protein level of P-Stat3 and IL1β in the spinal cord. (k) Co-immunofluorescence used to detect the phosphorylation of stats in astrocyte on the SDH, Scale bar = 100 um. Data are representative of three independent experiments and shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

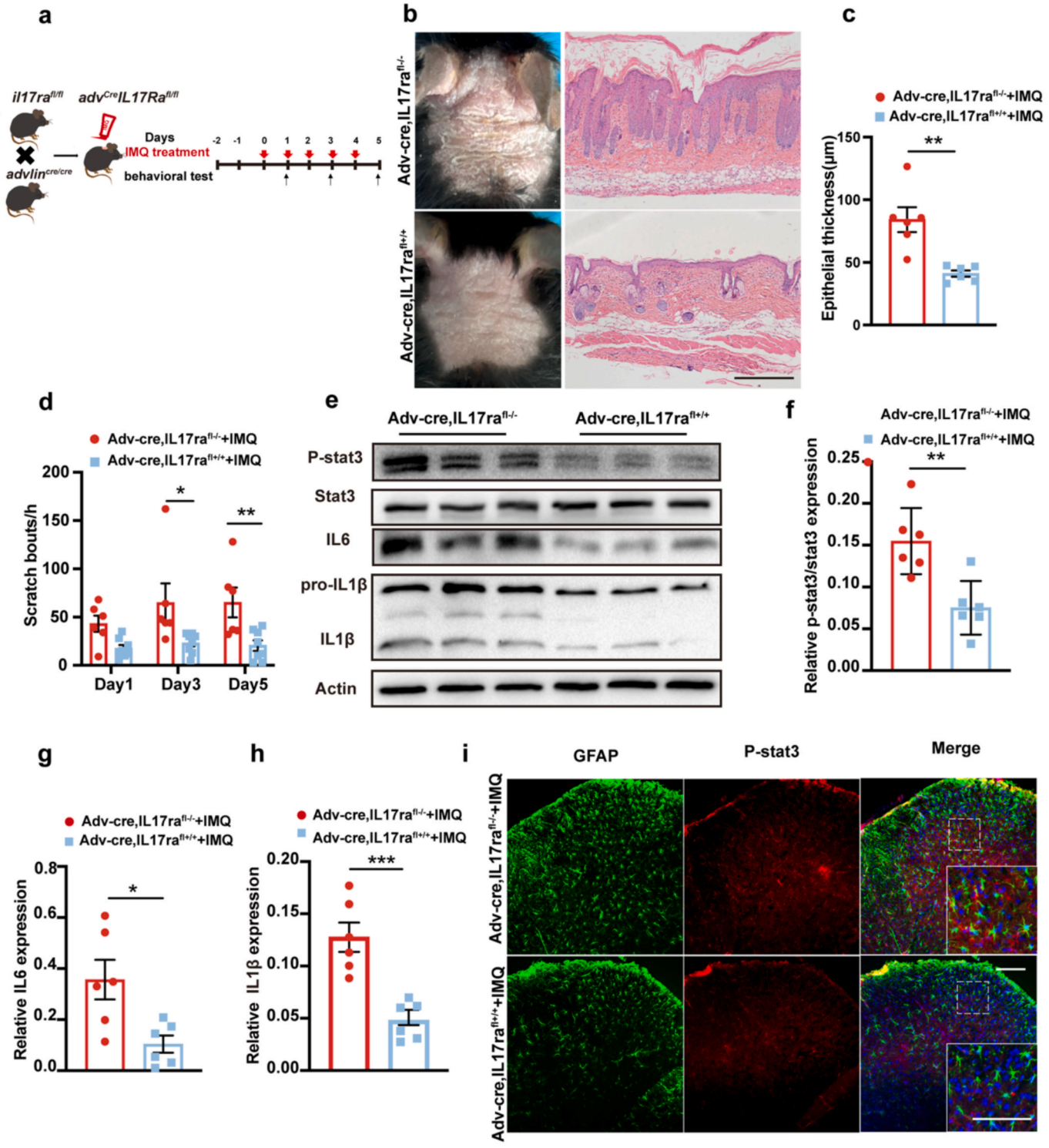

Fig. 6. The IL-17Ra on DRG neurons is vital in psoriasis-associated chronic itching (a) Flow chart of the conduct IMQ induced psoriasis with adv^{Cre}IL17Ra$^{fl/fl}$ mice. (b) Photograph of mouse back skin and HE stained of mouse skin is shown below. Scale bar = 100 um. (c) Epithelial thickness was measured according to the HE stains photos. (d) Evaluation of the number of spontaneous scratching bouts of mice on day 5. (e, f, g, h) Western blotting used to detected the protein level of P-Stat3, Stat3, IL-6 and IL-1β within the spinal cord. (i) immunofluorescence used to detect the expression P-Stat3 in astrocyte in the SDH. Data are representative of three independent experiments and shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001; ns, not significant.

peptide receptor-positive (GRPR^{+}) neuronal activation and the exacerbation of pruritus in psoriatic models(Liu et al., 2023). Next, we administered S3I-201, a specific inhibitor of Stat3, to IL6 treated astrocytes. As anticipated, 20 μM S3I-201 significantly suppressed IL-1β expression and the phosphorylation of Stat3 in astrocytes induced by IL-6 (Figs. 4f, g, h), suggesting that the IL-6-Stat3 pathway regulate IL-1β expression in astrocytes within the SDH to amplify chronic itch in psoriasis.

To model neuron-astrocyte crosstalk, we established a transwell co-culture system containing IL-17a-stimulated DRG neurons (upper chamber) and astrocytes (lower chamber) (Fig. 4i). Our findings indicated that IL-17a alone failed to activate astrocytic Stat3 signaling, and

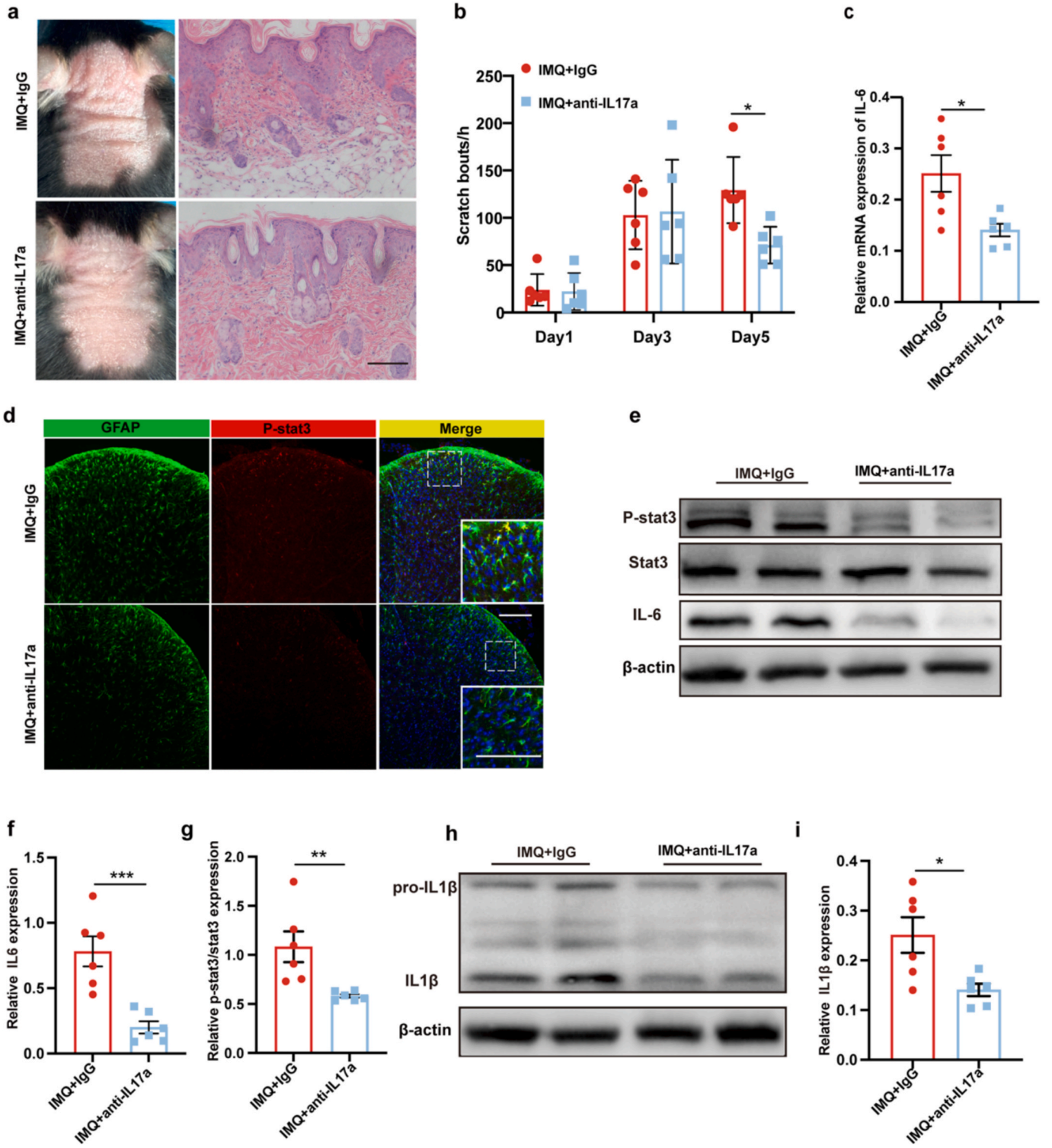

Fig. 7. IL-17a promote the chronic itch in IMQ- induced psoriasis. (a) Representative photograph of mouse back skin and HE stained of mouse skin are shown below. Scale bar = 100 um. (b) The effect of anti-IL-17a (10 mg/kg) on chronic scratching behavior induced by IMQ in mice. (c) q-PCR detected the IL-6 mRNA level in DRG tissue. (d) Co-immunofluorescence used to detect the P-Stat3 level in astrocyte. (e-g) IL-6, P-Stat3 and Stat3 level in spinal cord was detected by western blotting. (h-i) Western blotting detected the IL1β level in the spinal cord. Data are representative of three independent experiments and shown as mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ns, not significant.

co-culture with IL-17a-primed neurons significantly enhanced astrocytic P-Stat3 levels, an effect that was abrogated by IL-6 neutralization (Figure j, k). Additionally, IL-17a stimulated the expression of IL-1β in in co-cultured astrocytes, which was similarly suppressed by anti-IL-6 treatment (Figs. 4j, l, m).

Moreover, we investigated alterations in IL-1β levels within the spinal cord of mice. Our findings revealed that IL-17a administration and IMQ treatment both led to an elevation in IL-1β expression in the spinal cord of mice (Fig. S2a, b). Furthermore, functional blockade via administration of anti-IL-1β significantly attenuated chronic scratching

behaviors in psoriatic mice (Fig. S2c), while preserving acute itch responses to chloroquine and histamine (Fig. S2d, e). Therefore, it is speculated that IL-6 upregulation in the DRG tissue may exacerbate chronic itchiness in psoriasis by promoting IL-1β secretion via the activation of the Stat3 pathway in astrocytes within the SDH.

3.5. IL-6 knockdown in DRG neurons attenuated Psoriasis-Associated chronic itch

To elucidate the functional role of DRG-derived IL-6 in psoriatic itch pathogenesis, we developed a neuron-specific IL-6 knockdown model using an AAV vector (serotype 9), carrying short hairpin RNA against IL-6 (shIL-6) under the control of the human synapsin-1 (hSyn) promoter with enhanced green fluorescent protein (EGFP) as a transduction reporter (Figs. 5a, b). Systemic AAV delivery achieved selective neuronal transduction, as evidenced by EGFP fluorescence predominantly localizing to the DRG neuronal soma (Fig. 5c). The qPCR results confirmed a reduction in *IL-6* mRNA in the DRG tissues of shIL-6 mice compared to that in shRNA controls (Fig. 5d). Mice were subjected to either IMQ or intracutaneous IL-17a administration. These findings indicated a significant reduction in chronic itching and a marked alleviation of skin inflammation induced by IMQ in shIL-6 mice (Figs. 5e, f, g). Mechanistically, IL-6 knockdown abolished IMQ or IL17a stimulus-induced elevation of P-Stat3 and IL-1β overexpression in spinal cord tissues (Fig. 5h-j). Additionally, the proliferation and activation of astrocytes in the SDH induced by IMQ or IL-17a were also significantly reversed by the shIL-6 injection (Fig. 5k). These outcomes further suggest the crucial involvement of IL-6 derived from DRG neurons in the proliferation and activation of astrocytes, as well as in the development of psoriatic chronic itch.

3.6. IL-17Ra in DRG neurons mediated Psoriasis-Associated chronic itch

To investigate the potential role of IL-17a in promoting chronic itching in psoriasis by regulating IL-6 in DRG tissues, we re-analyzed a single-cell sequencing dataset of mouse DRG tissues (Zeisel et al., 2018). Our analysis revealed widespread expression of IL-17a-related receptors (IL17Ra, IL17Rc, and IL17Rd) across DRG neurons. Notably, IL-17Ra and IL-6 exhibited highly similar distribution patterns, with both predominantly localized in peptidergic neurons (Fig. S3a). Immunofluorescence staining further confirmed substantial colocalization of IL-17Ra and IL-6 in DRG neurons (Fig. S3b). Moreover, quantitative analysis demonstrated significant upregulation of IL-17Ra mRNA levels in the DRG tissues of IMQ-treated mice (Fig. S3c). Consequently, we proposed that the upregulation of IL-17a in psoriatic skin tissues may affect IL-6 expression in DRG tissues via IL-17Ra signaling.

Accordingly, we generated advillin-Cre, IL-17Ra$^{fl/fl}$ (advCre, IL-17Ra$^{fl/fl}$) mice with conditional knockout of IL-17Ra in peripheral sensory neurons (Fig. 6a, S4a, b). Neuronal IL-17Ra ablation resulted in marked attenuation of IMQ-induced skin lesions and a significant reduction in chronic itching behavior (Figs. 6b, c, d). Furthermore, IL-17Ra deletion in sensory neurons significantly downregulated the IL-6 levels in the DRG tissue of mice treated with IMQ (Fig. S4b, c, d). Additionally, the expression of IL-6 in the spinal cord tissue of IMQ-treated mice was markedly reduced following the deletion of IL-17Ra in sensory neurons, resulting in hindered astrocyte proliferation and activation, as well as reduced IL-1β expression in the spinal cord (Figs. 6e, f, g, h, i). Together, these data indicate that the high levels of IL-17a in the skin of psoriasis significantly contribute to chronic itch development by modulating IL-6 expression through IL-17Ra in sensory neurons.

3.7. Anti-IL-17a therapy Modulates sensory neuron IL-6 signaling and Alleviates psoriatic pruritus

To evaluate the therapeutic potential of IL-17a blockade, we intracutaneously administered anti-IL-17a to IMQ-induced psoriatic mice. While the treatment significantly attenuated chronic itch behavior, it did not markedly improve psoriasis-like skin lesions, potentially due to suboptimal dosing (Figs. 7a, b). Importantly, intracutaneous anti-IL-17a delivery effectively suppressed IL-6 overexpression in DRG neurons, demonstrating its capacity to modulate neuron-specific IL-6 signaling (Fig. 7c) Additionally, anti-IL-17a treatment reversed IMQ-induced astrocyte activation and proliferation and IL-6 expression levels in the SDH (Fig. 7d-g). Notably, anti-IL-17a administration also led to a significant downregulation of IL-1β expression in the spinal cord (Fig. 7h-i). These findings provide mechanistic evidence supporting IL-17a blockade as a potential therapeutic strategy for psoriatic pruritus, particularly through its modulation of the DRG neuron-spinal cord IL-6/IL-1β signaling axis.

4. Discussion

The pruritus-scratch cycle represents a critical clinical challenge in psoriasis, not only compromising patient's quality of life, but also perpetuating inflammatory skin damage through mechanical trauma (Reich et al., 2016). Anti-IL-17a therapies are effective for treating psoriasis (Ly et al., 2019). Moreover, clinical reports have also demonstrated the efficacy of IL-17a antagonists in alleviating psoriatic itch (Gottlieb et al., 2018), however, their therapeutic benefits for pruritus remain mechanistically undefined. Previous studies have highlighted the role of IL-17a in inducing pain (Chen et al., 2022; Luo et al., 2021). Studies have showed that IL-17a could not induce acute scratching responses or regulate acute itch, induced by histamine and chloroquine, similar to our results (Pavlenko et al., 2020; Stull et al., 2016). Quite remarkably, our study displays that IL-17a intensifies chronic itch associated with psoriasis, which provides a theoretical foundation for the potential use of anti-IL-17a therapy in managing psoriasis-related pruritus.

Emerging evidence has highlighted the multifaceted role of neuronal IL-6 in mediating neuroimmune crosstalk. A prior investigation demonstrated that IL-6 released from DRG neurons has the potential to stimulate astrocytes in the spinal cord, thereby exacerbating chronic itch (Stull et al., 2016), we identified IL-17a as an upstream regulator of this pathway. We postulated that elevated cutaneous IL-17a in psoriasis engages IL-17Ra in sensory neurons, driving IL-6 overproduction in the DRGs. Elevated IL-6 levels in sensory neurons functions as a critical signal for the escalation of chronic itching. Moreover, IL-6 from sensory neurons can be released into the peripheral tissues to modulate peripheral immune responses. IL-6 produced by sensory neurons can be transported via axoplasmic transport to local cardiac tissues, promoting ventricular remodeling after myocardial infarction (Sun et al., 2024). In addition, enteric neurons secrete IL-6 to inhibit the differentiation of Treg cells to regulate the microbial-immune homeostasis in the intestine (Yan et al., 2021). In this study, the knockdown of IL-6 in DRG neurons suppressed pruritus in psoriatic mice and significantly reduced cutaneous inflammation. Nevertheless, additional research is required to elucidate whether this effect is attributable to diminished scratching behavior or alterations in neuroimmune regulatory pathways.

Several studies have implicated spinal astrocytes in the development of chronic itching. Reactive astrogliosis in the SDH has been observed in various chronic dermatosis mouse models, including dry skin (Benarroch, 2022), atopic dermatitis (Shiratori-Hayashi et al., 2015), and contact dermatitis (Koga et al., 2020; Shiratori-Hayashi et al., 2015). Our study extends these observations to psoriatic pruritus, demonstrating that SDH astrogliosis occurs in IMQ-induced psoriasis models and that pharmacological astrocyte inhibition via LAA attenuates chronic itching. The pruritogenic capacity of reactive astrocytes stems from their ability to release neuromodulators, including glutamate, ATP, and cytokines, which enhance nociceptor excitability (Benarroch, 2022). Stat3-dependent Lcn2 secretion has also been implicated in astrocyte-mediated potentiation of chronic itch in chronic

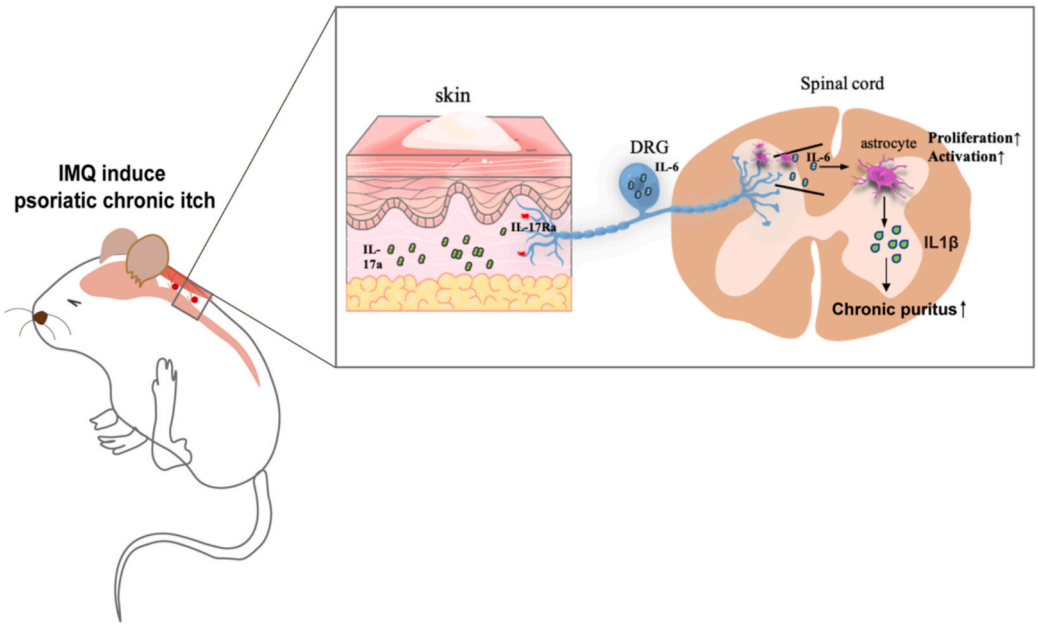

Fig. 8. The following diagram illustrates the mechanism by which IL-17a contributes to chronic itch in psoriasis. IL-17a, elevated in psoriatic skin, activates IL17ra on sensory nerve fibers, leading to the increased release of IL-6 into the SDH. IL-6 subsequently promotes the proliferation and activation of astrocytes, which release IL-1β, thereby exacerbating chronic itch.

dermatitis. However, our findings reveal a divergent mechanism in psoriasis, where IL-6-stimulated astrocytes preferentially secrete IL-1β rather than Lcn2. The IL-1β secreted by glial cells has been demonstrated to mediate the sensitization of $GRPR^+$ neurons in the SDH, thereby promoting chronic itch in psoriasis(Liu et al., 2023), $GRPR^+$ neurons in the SDH a pivotal role in transmitting peripheral itch signals to the brain by binding to the itch-specific neuropeptide gastrin-releasing peptide (GRP)(Chen, 2021). Which indicated the IL-1β also role as a neuromodulator secreted by activated astrocyte to amplify the chronic itch signal in the SDH. Additionally, our study confirms that intrathecal injection of anti-IL-1β significantly inhibits the scratching behavior in psoriatic mouse model. Nonetheless, it is conceivable that activated astrocytes may also affect chronic itching via alternative pathways.

IL-17a exerts its biological effects through heterodimeric receptor complexes, primarily pairing subunit A with subunit C (IL-17Ra/Rc) or subunit A with subunit D (IL-17Ra/Rd)(Su et al., 2019). Our reanalysis of murine DRG single-cell sequencing data revealed broad neuronal expression of IL-17 receptor isoforms (IL-17Ra, Rc, Rd, and Re), with IL-17Ra showing striking spatial colocalization with IL-6 in peptidergic sensory neurons. Consequently, we knock down IL-17Ra in sensory neurons to substantiate its role in chronic itching in psoriasis. As hypothesized, the deletion of IL-17Ra in sensory neurons led to a significant decrease in chronic itch induced by IMQ as well as a reversal of the heightened expression of IL-6 in DRG tissues. Subsequent experiments revealed that IL-17Ra deletion in sensory neurons effectively suppressed the IMQ-induced proliferation and activation of astrocytes.

5. Conclusions

Overall, our research delineated a neurocutaneous signaling axis central to psoriatic pruritus and elucidated the significant impact of IL-17Ra on sensory neurons in driving chronic itching in psoriasis. Specifically, we found that IL-17a, which is elevated in psoriatic skin tissues, can promote the release of IL-6 via IL-17Ra in sensory neurons, leading to the proliferation and activation of astrocytes in the SDH. These activated astrocytes secrete more IL-1β to heighten the sensitivity of itch-transmitting neurons, thereby exacerbating the chronic itching of psoriasis (Fig. 8). To our knowledge, this study is the first to provide the mechanistic evidence that $IL\text{-}17Ra^+$ sensory neurons are critical gatekeepers of psoriasis-associated neuroimmune communication from skin to the spinal cord. Our results identify novel therapeutic nodes for disrupting the pathogenic itch-scratch loop in chronic inflammatory skin diseases, offering novel therapeutic targets for disrupting the self-perpetuating itch-scratch cycle in psoriasis.

Author contributions

H.C and M.L conceived the studies and supervised the research. X.L and J.J designed the studies. X.L, S.L, Q.G, O.Z, B.C and Y.Y conducted experiments and analyzed data. S.L, J.Z and Q.T fed and identified mice. X.L wrote the manuscript. All authors reviewed the manuscript. H.C final approval of the version to be submitted.

CRediT authorship contribution statement

Xin Liu: Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Jian Jiang:** Methodology, Data curation. **Shiying Lin:** Writing – review & editing, Investigation, Data curation. **Wenqiang Ge:** Methodology. **Qingxiao Tao:** Formal analysis. **Suwen Liu:** Formal analysis. **Ouyang Zhanmu:** . **Yang Yang:** . **Bao Chai:** . **Jingyu Zhang:** Methodology. **Man Li:** Writing – review & editing, Supervision, Methodology. **Hongxiang Chen:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.106218.

Data availability

All data are available in the main text or the supplementary materials.

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