THE EFFECT OF SECUKINUMAB ON TRAF6 EXPRESSION AND REDUCTION OF MYELOID-DERIVED SUPPRESSOR CELLS IN PSORIASIS RATS

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ABSTRACT

This study investigated the mechanism by which secukinumab (SEC) targeted tumor necrosis factor receptor-associated factor 6 (TRAF6) to regulate myeloid-derived suppressor cells (MDSCs) in psoriatic rats. Fifteen male rats were randomly divided into three groups (n=5): Blank group (received intragastric administration of normal saline), Model group (after being established as a psoriasis model, received intravenous injection of normal saline) and SEC group (received intravenous administration of SEC after modeling). The Psoriasis Area and Severity Index (PASI) score was evaluated. Splenic MDSCs, serum cytokine levels, and the expressions of TRAF6, arginase 1 (Arg1), and inducible nitric oxide synthase (iNOS) were measured. Compared with the Blank group, body weight of rats in both Model group and SEC group was greatly reduced ($P \leq 0.05$). Compared with the Model group, the SEC group showed a significantly decreased PASI score ($P \leq 0.05$), reduced serum cytokine levels, a lower proportion of splenic MDSCs, and downregulated expressions of TRAF6, Arg1, and iNOS. In a psoriasis rat model, the therapeutic effect of SEC is associated with reduced expression of TRAF6 and a decrease in MDSCs.

Keywords: secukinumab; psoriasis; TRAF6; myeloid-derived suppressor cells

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INTRODUCTION

Psoriasis may also involve joints in severe cases (Sugumaran *et al*., 2024). The etiology of the disease is mainly due to a combination of genetic, environmental, infectious, and psychological factors; the detailed pathogenesis remains poorly understood. After investigating the cause of psoriasis, it was found that the IL-23/IL-17 inflammatory axis is the main culprit. (Maronese *et al*., 2024) IL-23 acts on and maintains the function of Th17. The activated cells secrete lots of different cytokines like IL - 17 A. The IL-17A has effects upon keratinocytes, fibroblasts, and endothelial cells of the skin, resulting in many inflammatory reactions leading to typical manifestations of psoriasis (Fischer *et al*., 2023; Peng *et al*., 2024). The current first line of therapy for Psoriasis, such as corticosteroids, Vitamin D3 analogues, and Retinoids, all inhibit the proliferation/differentiation of keratinocytes and also the activation of T-Cells. (Pixley *et al*., 2023; Marchlewicz *et al*., 2024) (Wang *et al*. 2023; Yu *et al*. 2024). Out of which the SEC is very specific, and it binds to IL-17A and blocks the ligand from binding to cell surface receptors. It can inhibit hyperplasia of keratinocytes and stop the inflammatory cells from migrating to skin tissues to make the outermost layer of skin stronger (Snyder *et al*. 2023)

Psoriasis was an autoimmune skin disease; the immune response was primarily mediated by T cells; among these, CD4+ Th cells and CD8+ T cells were primarily involved. TRAF6 was a key mediator of the innate immune response, antigen receptor signaling, and pro-inflammatory pathways (Wang *et al*., 2024). Thus, besides the IL-23/IL-17 inflammatory axis, TRAF6 overexpression was also related to the occurrence and development of psoriasis (Yuan *et al*., 2023; Chung *et al*., 2025). Meanwhile, myeloid-derived suppressor cells (MDSCs) have strong immunosuppressive properties. They have been shown to promote tumor growth by migrating to tumor sites and secreting active molecules that inhibit immune cell activity (Lasser *et al*., 2024). Evidence also shows an abnormal increase in MDSCs in the peripheral blood of patients with psoriasis, where they exert immunosuppressive effects, although the underlying mechanism remains unclear (Balderas-Miranda *et al*., 2026).

Although we are aware that it will be feasible for secukinumab to improve the condition of people suffering from psoriasis by inhibiting IL-17A, but do not know whether secukinumab affects the deep-node at a deeper level on this circuit like TRAF6 pathway or innate-immunity cells other than T cells-MDSCs Recently some studies have shown that there is an excessive accumulation of MDSCs and unusual expression of TRAF6 in the peripheral blood of psoriasis

patients, it can participate in continuous inflammatory. But it cannot be proved directly that blocking IL-17A makes a difference in how MDSCs suppress the immune system, according to TRAF6. So we made a psoriasis rat model to get out of just thinking about the old IL17A axis kind of way. It's looking into whether secukinumab changes the immune micro-environment by cutting down on TRAF6 and MDSC cells, along with all sorts of things that they make, like Arg1, iNOS.

MATERIALS AND METHODS

Psoriasis-like skin model and grouping: There were fifteen SPF-Sprague Dawley male rats, 8-weeks old and weighing 200~260 g, which were purchased from Hunan Silaike Jingda Experimental Animal Co., Ltd., China. All animal experiment protocols have been approved by the Institutional Animal Care and Use Committee of Hangzhou Normal University (No. 2024148), which should comply with all the rules. The rat kept in (23±2) ˚C temperature with a humidity level of (50±3) %. The period of lights and darkness is 12/12. The depilatory cream was used to remove the tiny hair from the backs of all the rats. The duration was 14 days. The rats were randomly separated into three groups as following:

Blank group (n=5): Topical administration of Vaseline (Unilever, USA) was performed on all the dorsal skin once a day for 14 times. After that, normal saline (20mL/kg) was given orally by gavage once a day for the next 7 days.

Model group (n=5): Rats were given 20% rhubarb decoction (Anhui Dongsheng Youbang Pharmaceutical Co., Ltd., China) at a dose of 20 mL/kg by oral gavage once daily. Meanwhile, 5% imiquimod cream (Hubei Keyi Pharmaceutical Co., Ltd., China) was applied evenly on the dorsal skin at a dose of 0.05 g/cm² once daily for 14 consecutive days to establish a psoriasis-like dermatitis model. After model establishment, normal saline (0.5 mL/100 g) was injected intravenously once daily for 7 consecutive days.

SEC group (n=5): Rats were also treated the same way as the Model group. And then we gave them an intravenous injection of 27.03 mg/kg secukinumab injection (Novartis Pharmaceuticals, China) every day for 7 days: Dose justification: The clinical daily dosage of secukinumab in adults is 300mg. According to the standard body weight for an adult of 70kg, then it would be 300/70 = ~4.29 mg/kg. According to the equivalent dose ratio table, we found that it should be about 6.3 times the human clinical dose, which is: 6.3×4.29 = 27.03mg/kg. But the human pharmacokinetics is very different from that of rats: Also, for instance, it's usually more in rats than in humans. And then the half-life is short as well; so secukinumab is like 15-30 days for humans, but much lower in rodents. Furthermore, there were species differences in the FcRn-mediated antibody recycling process. So even though it's equal at 27.03 mg/kg when converting for BSA, it does not mean that the *in vivo* exposures will all be equivalent to human therapeutic levels, like AUC or Cmax. Selected doses mostly come from the use of the same biological agent for rats' inflammatory model before, and combining it with some preliminary effects, such as safety period and effectiveness, to make the experiment result have a certain detectable biological effect after a long time. Also, in the future, we could possibly optimize doses through PK-PD models.

Bodyweight change and symptom changes were observed every day. For a successful model, there were symptoms of erythema, scale, and thickening of the skin on the back of the rats in the Model and SEC groups. The body weight of each rat was recorded every day. Back skin lesions (erythema, scaling, skin thickening) were assessed by two equally trained and blinded assessors. Modeling success was defined by a Psoriasis Area and Severity Index (PASI) score where any one score (erythema, scaling, or infiltration) was ≥ 2 and the total score was ≥ 4. All 10 rats subjected to modeling (5 in the Model group and 5 in the SEC group) were successful by day 7. Inter-observer agreement was good ($\kappa = 0.86$; 95% CI: 0.78–0.94).

PASI scoring: On days 1, 7, and 14, dorsal skin lesions of rats were photographed and scored according to the PASI criteria (Maravilla-Herrera *et al*., 2023) for erythema, skin thickness, and scaling severity: i) Erythema: 0 point for smooth skin with no erythema; 1 point for slight redness; 2 points for moderate redness; 3 points for severe redness; 4 points for severe redness accompanied by weight loss. ii) Skin thickness: 0 point for smooth skin without folds; 1 point for slight folds at the edges; 2 points for mild folds; 3 points for pronounced folds; 4 points for pronounced folds accompanied by weight loss. iii) Scaling: 0 point for smooth skin without scales; 1 point for slight scaling; 2 points for moderate scaling; 3 points for severe scaling; 4 points for severe scaling accompanied by weight loss. PASI score = (erythema score + skin thickness score + scaling score), with a total score ranging from 0 to 12. Five rats were assigned to each group in this study, with a total of 15 rats, and all animals were included in the analysis. Clinical scoring was performed by two observers in a blinded manner. On day 7, all 10 rats in the Model and SEC groups successfully developed typical skin lesions.

Enzyme-linked immunosorbent assay: 24h after the last intervention, rats were anesthetized by intraperitoneal injection of 30 mg/kg 3% sodium pentobarbital (Thermo Fisher, USA). Anesthesia depth was confirmed by the loss of

the righting reflex, and all procedures were conducted with the principle of minimizing animal distress. Blood (8 mL per rat) was collected from the abdominal aorta and left at 25°C for 1h, centrifuged at 1500 rpm/min for 15min. Supernatant serum was stored at -80°C. Serum interleukin-12 p70 (IL-12p70), IL-17A, and interferon (IFN)-γ were measured utilizing a two-antibody sandwich ELISA (Thermo Fisher, USA). Standard, sample, and blank wells were set up. Standard wells received 50μL of standard solutions, sample wells received 10μL of test sample plus 40μL of diluent, and blank wells received no additions. Except for blank wells, 100μL of HRP-labeled detection antibody was applied. After sealing, the plate was incubated in 37°Cwater bath for 1h. Liquid was discarded from all wells, and the plate was washed five times. Then, 50μL each of substrate A and B was applied at 37°C in the dark for 15min. 50μL of stop solution was utilized, and the absorbance (OD value) was measured within 15min employing a UV5 ultraviolet spectrophotometer (Mettler Toledo, Switzerland).

Flow cytometry: Spleen samples from each group of rats were placed in phosphate-buffered saline (Thermo Fisher, USA) + 0.2% FBS (Gibco, USA) for lysis and extraction of mononuclear cells. Cells were then seeded in RPMI-1640 (Gibco, USA) and stimulated with 50ng/mL phorbol 12-myristate 13-acetate (Thermo Fisher, China) and 1 μg/mL ionomycin (Thermo Fisher, USA). Cell density was adjusted to 1×10^7 cells/mL, centrifuged at 1000 rpm/min for 5min. Cells were resuspended in PBS (Thermo Fisher, USA) and stained with anti-mouse CD11b-PE antibody (Biolegend, USA) and anti-mouse Gr-1-FITC antibody (Biolegend, USA). After incubation at 4°C in the dark for 30min, the cells were centrifuged at 1000 rpm/min for 5min to separate the supernatant. Cells were rinsed with PBS, fixed with 4% paraformaldehyde (Thermo Fisher, USA), and analyzed employing a CytExpert flow cytometer (Beckman Coulter, USA) to determine the proportion of MDSCs. $CD11b^+Gr\text{-}1^+$ cells were MDSCs. However, in existing rat immunological studies, because commercially available rat-specific Ly6C/Ly6G antibodies were lacking, this study still used anti-mouse Gr-1 antibodies (such as clone RB6-8C5) that had been verified to cross-react with rat antigens to identify MDSC-like cells. The anti-mouse Gr-1-FITC antibody used in this study was clearly indicated in its product datasheet to cross-react with the homologous rat Ly6C/G molecules.

Quantitative real-time PCR: The blood collected from all the rats was sacrificed, and then the dorsal lesions' skin was rapidly excised. Following rinsing with physiological saline, a portion of the tissue was retained, while the remainder was homogenized and divided into two aliquots. One aliquot of skin tissue homogenate was employed for total RNA extraction with Trizol reagent (Thermo Fisher, USA). Concentration and purity of RNA were measured using a NanoDrop2000c nucleic acid detector (Thermo Fisher, USA). Subsequently, first-strand cDNA was synthesized via PrimeScript™ kit (Perfect Real Time) (Beijing Baori Co., Ltd., China). Using cDNA as the template, mRNA levels of GAPDH, TRAF6, and the MDSC effector molecules Arg1 and iNOS were detected via TB Green® Premix Ex Taq™ II (Tli RNaseH Plus), Bulk kit (Beijing Baori Medical Biotechnology Co., Ltd., China). The reaction program was: 95°C for 30s; 40 cycles of 95°C for 5s and 60°C for 30s. GAPDH was employed as the internal reference gene, and relative mRNA levels of TRAF6, Arg1, and iNOS were computed using the $2^{-\Delta\Delta CT}$ assay.

Western blotting: The other aliquot of skin tissues' homogenate was utilized to extract the total protein with RIPA buffer (Thermo Fisher, USA). Determine the protein amount with BCA (Beyotime Biotech, China), and do SDS - PAGE. The separated proteins were added to the PVDF Membrane (Beyotime Biotech, China). Then it has been incubated on skimmed milk (Beyotime Biotech, China), 25 degrees Celsius for one hour. The membrane was washed and incubated with the primary antibody at 4℃ for 12h; it was rabbit monoclonal TRAF6 (1:5000), rabbit polyclonal Arg1 (1:3000), rabbit monoclonal iNOS (1:1000), and mouse monoclonal β-actin (1:5000) (all purchased from Abcam, UK). It was washed after that, incubated with HRP anti-rabbit IgG (1:5000; Abcam, UK) at 25°C for 2h. The membrane, after being finally washed, was developed with Electro-Chemiluminescence Reagents (Beyotime Biotech, China), and then it was photographed by GELDOC Go (Bio-Rad, USA). The gray level of each band was measured by using ImageJ software (NIH, USA), and then it was normalized based on the amount of β-actin. It has made sure that there will be no change in the internal reference by carrying out a one-way analysis of variance (One-way ANOVA) on the β-actin between groups.

Statistical analysis: All the results are presented with mean and Standard Deviation (x±s). All statistics were done through SPSS 26.0. Firstly, we carried out normality test (Shapiro-Wilks method) and homogeneity of variance test (Levene method) for the data in every group: The results found that all met a normal distribution (P>0.05), and also had homogeneity of variance (P>0.05). So one-way ANOVA (one-way ANOVA) was carried out to see the difference between several groups. Since we had planned ahead of time that the comparison would solely be between the Model group vs the blank control group, and the SEC group vs the Model group, there being so few groups (k=3), I employed the LSD method, which assumes homogeneity of variances for post hoc pair-wise comparisons. Statistically significant if the $P \leq 0.05$.

RESULTS

Body weight of rats in each group: In Figure 1, the body weight of rats in the Blank, Model, and SEC groups increases with the passage of time. The Blank group had the highest increase in weight, more than double that of the Model and SEC groups ($P \leq 0.05$). The body weight of the Model and SEC group has a very small difference ($P > 0.05$).

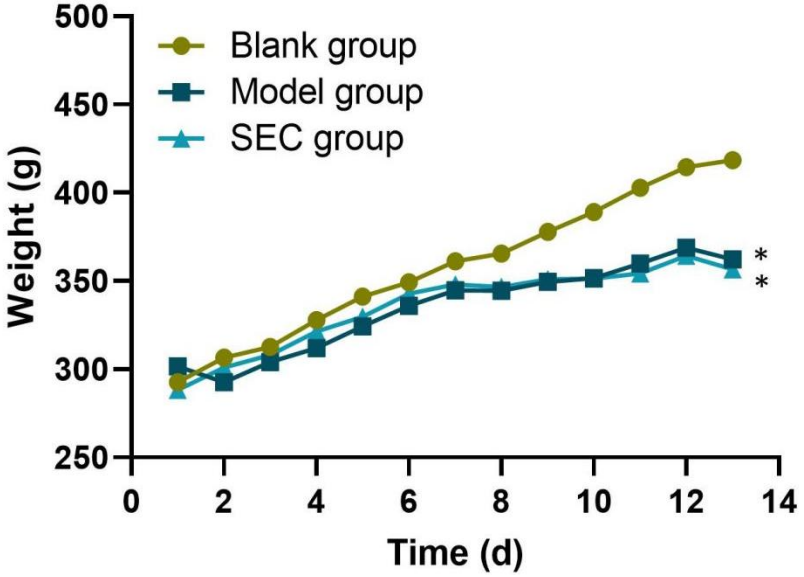

Figure 1. Body weight changes in rats from each group after treatment. *$P \leq 0.05$ *vs*. Blank group; #$P \leq 0.05$ *vs*. Model group.

Differences in PASI scores among groups: In Figure 2A, on day 1 model no change can be seen in the targeted skin areas of the rats from the Blank, Model, and SEC groups. On days 7 and 14 of the modeling, there was no difference between the Blank group's target skin area, but erythema, scales, and thickening were observed in both the Model and SEC groups; however, these lesions were less severe in the SEC group than in the Model group. On day 1 of modeling, the PASI score of was 0 in every group. And from Figure 2B-C, on days 7 and 14 of the modeling, the PASI scores of the SEC group are lower than those of Model group ($P \leq 0.05$).

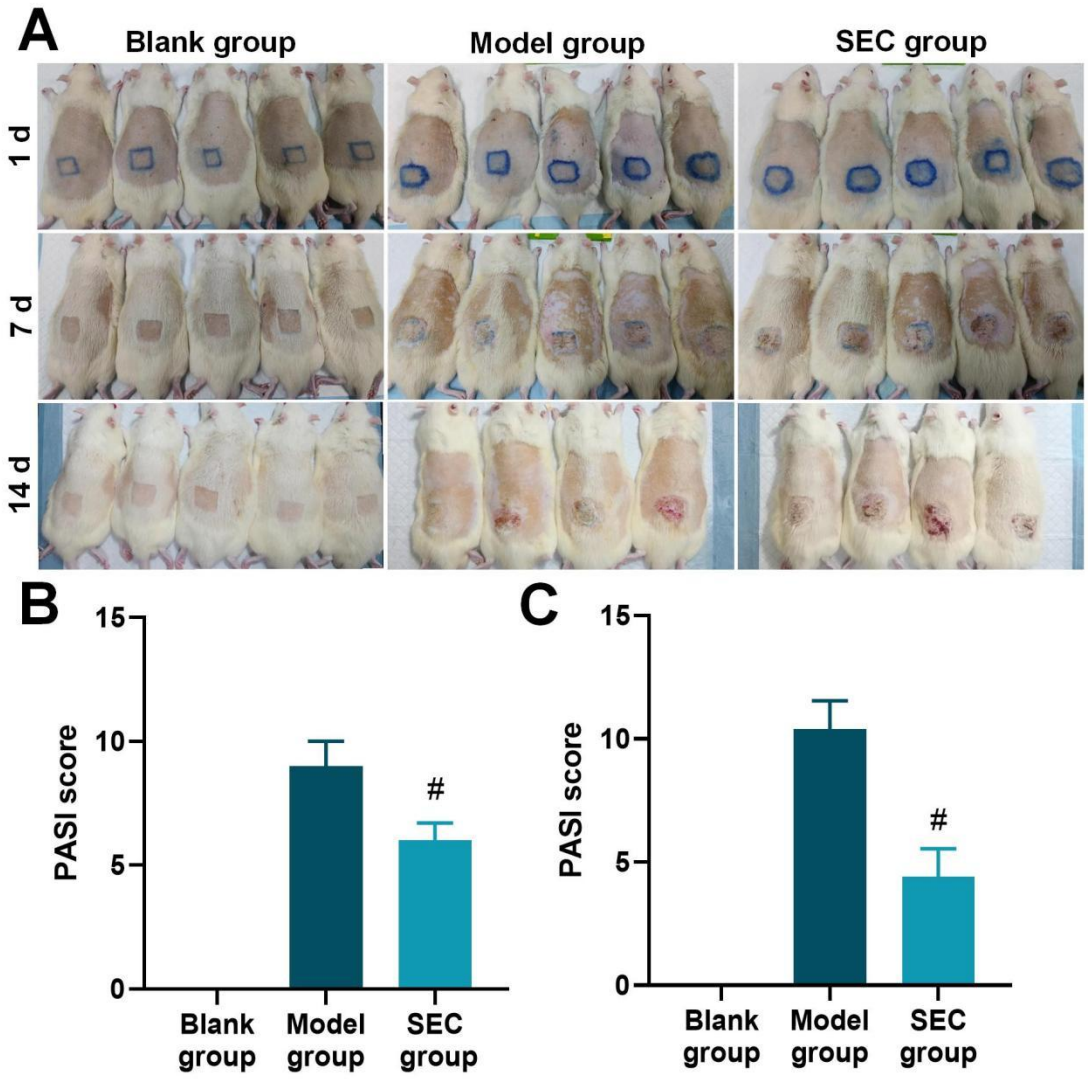

Figure 2. Comparison of PASI scores in rats from each group after treatment. (A) Skin observations of rats in each group on days 1, 7, and 14 after intervention; (B) PASI scores on day 7 after intervention; (C) PASI scores on day 14 after intervention. #$P \leq 0.05$ *vs*. Model group.

Serum IL-12p70, IL-17A, and IFN-γ levels among groups: As shown from Figure 3, compared with the Blank group, IL-12p70, IL-17A, and IFN-γ were all higher than those of the Model group ($P < 0.05$), and the SEC group was lower than that of the Model group ($P \leq 0.05$).

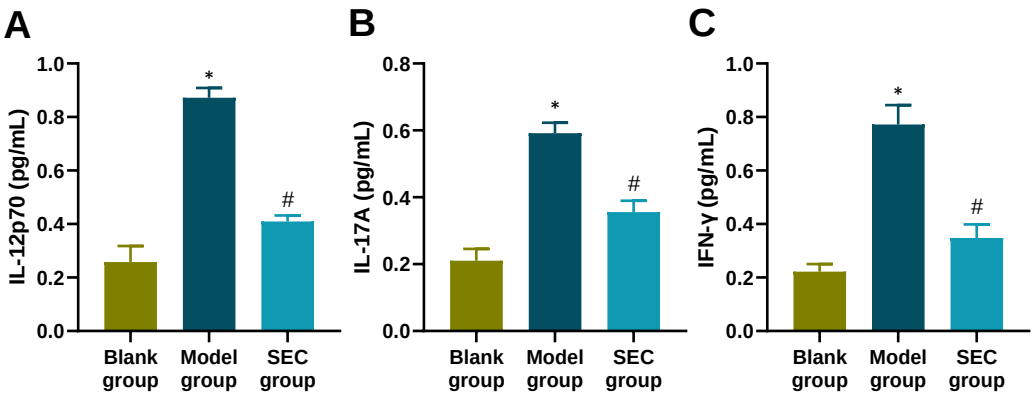

Figure 3. Comparison of serum IL-12p70, IL-17A, and IFN-γ in rats from each group. (A) IL-12p70; (B) IL-17A; (C) IFN-γ. #$P \leq 0.05$ *vs.* Model group.

The proportion of splenic MDSCs among groups: As we can see from Figure 4A, the ratio of MDSCs detected in the spleen of the Model group is much greater than that of Blank and SEC groups. Figure 4B Compared with the Blank group, the proportion of splenic MDSCs in the Model group is dramatically increased ($P < 0.05$). The proportion of splenic MDSCs in the SEC group is much less than that of the Model group ($P \leq 0.05$).

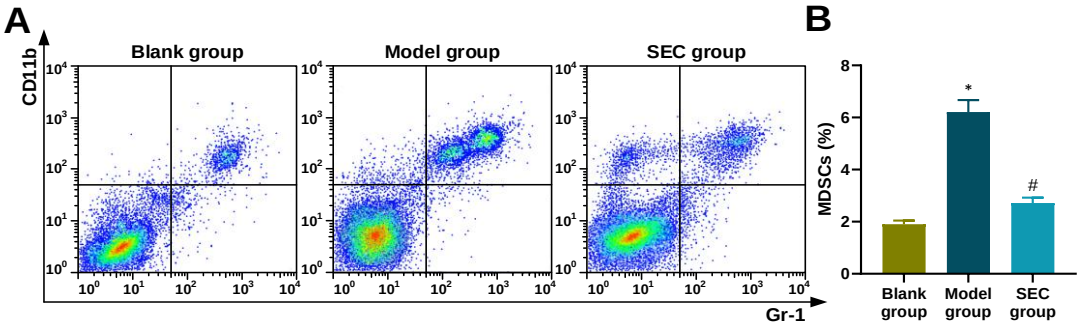

Figure 4. Comparison of splenic MDSC levels in rats from each group. (A) Proportion of splenic MDSCs detected by flow cytometry; (B) Comparison of the proportion of splenic MDSCs among groups. *$P \leq 0.05$ *vs.* Blank group; #$P \leq 0.05$ *vs.* Model group.

TRAF6, Arg1, and iNOS in skin among groups: In Figures 5A,5B, and 5C, compared with the Blank group, relative mRNA expression of TRAF6, Arg1, and iNOS of the target skin of the Model group was obviously higher($P \leq 0.05$), and relative mRNA levels of TRAF6, Arg1, and iNOS were significantly down in the SEC group ($P \leq 0.05$).

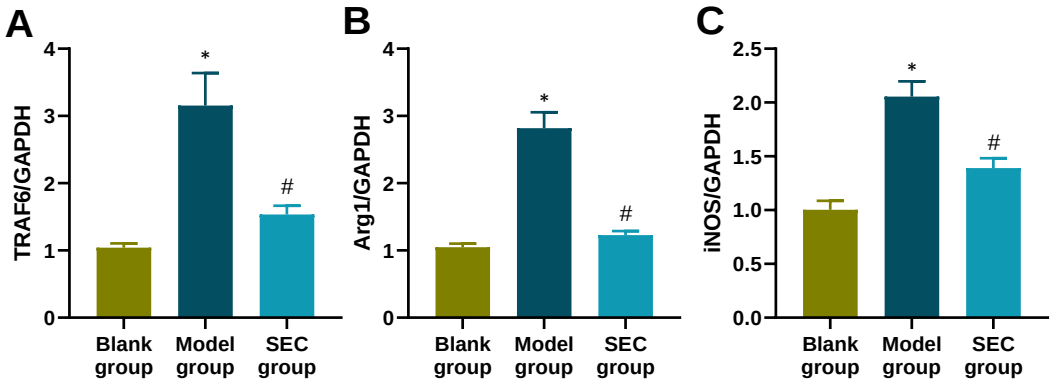

Figure 5. Comparison of TRAF6, Arg1, and iNOS mRNA levels in the skin of rats. (A) TRAF6; (B) Arg1; (C) iNOS. *$P \leq 0.05$ *vs.* Blank group; #$P \leq 0.05$ *vs.* Model group.

Figure 6A shows the protein expression of TRAF6, Arg1, and iNOS in the target skin tissue of rats in each group, detected by Western blot. Figure 6B-D were bar graphs of the relative protein expression levels of TRAF6, Arg1, and iNOS in each group, respectively. The results showed no significant difference in its expression ($P > 0.05$), which met the prerequisite for normalization. In Figure 6A, protein levels of TRAF6, Arg1, and iNOS in the target skin were highest in the Model group, followed by the SEC group. In Figures 6B-D, versus the Blank group, the relative protein levels of TRAF6, Arg1, and iNOS in the target skin of the Model group were notably elevated ($P \leq 0.05$), and were greatly decreased in the SEC group versus the Model group ($P \leq 0.05$).

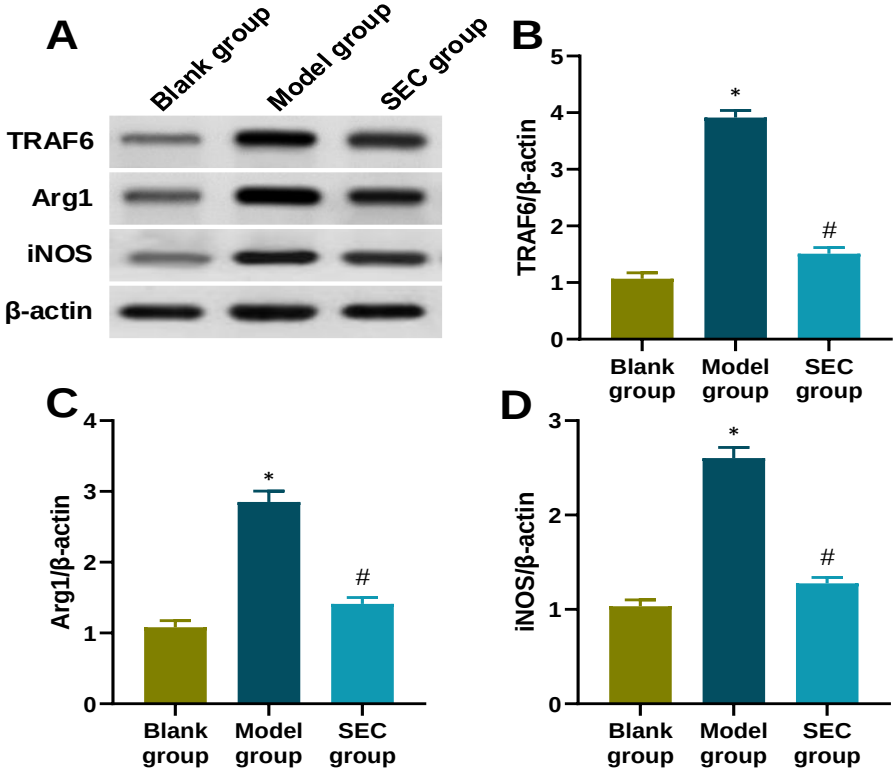

Figure 6. Comparison of TRAF6, Arg1, and iNOS protein levels in the skin of rats. (A) Western blot analysis; (B) Comparison of TRAF6 protein levels; (C) Comparison of Arg1 protein levels; (D) Comparison of iNOS protein levels. *$P \leq 0.05$ *vs.* Blank group; #$P \leq 0.05$ *vs.* Model group.

DISCUSSION

Psoriasis is characterized by persistent inflammation, where abnormal immune activation and aberrant keratin deposition collectively contribute to disease progression (Sugumaran *et al.*, 2024). Imiquimod cream, a ligand for Toll-like receptors, has been widely employed to induce psoriasis-like skin models in animals (Hseu *et al.*, 2023; Roy *et al.*, 2023). A psoriasis-like rat model was successfully established utilizing imiquimod cream. The modeled rats exhibited reduced body weight, along with notable erythema, scaling, and thickening in the target skin area, accompanied by a significant increase in PASI scores, indicating successful model induction. Secukinumab directly targets core inflammatory cytokine IL-17A, blocking its interaction with IL-17RA/RC cell surface receptors. This mechanism inhibits keratinocyte hyperproliferation and ameliorates inflammatory cell infiltration in lesions, ultimately reversing the pathological processes of psoriasis (Simopoulou *et al.*, 2023). Furthermore, this study observed that after secukinumab administration, the psoriasis-like rat model showed marked improvement in erythema, scaling, and skin thickening in the target area, along with a significant reduction in PASI scores.

IL-12p70, IL-17A, and IFN-γ are potential biological markers of psoriasis, primarily co-produced by Th1 cells, Th17 cells, and dermal dendritic cells, macrophages, and mast cells, among others (Ruscitti *et al.*, 2023). IL-12 is a common immunoregulatory factor that promotes Th1- and Th17-mediated inflammatory responses (Gargiulo *et al.*, 2021). Dermal dendritic cells can release IL-17A to stimulate epidermal hyperplasia, while IL-17A acts on epithelial

cells to regulate keratinocyte proliferation and abnormal differentiation (Fischer *et al*., 2023). Moreover, IL-17A specifically activates keratinocytes, prompting them to release inflammatory mediators and chemokines, thereby further inducing chemotaxis and activation of immune cells and amplifying the inflammatory response (Roy *et al*., 2023; Navarro-Compán *et al*., 2023). This study found significantly elevated IL-12p70, IL-17A, and IFN-γ in the psoriasis-like rat model, indicating enhanced systemic inflammation. Furthermore, secukinumab considerably reduced IL-12p70, IL-17A, and IFN-γ in model rats. These results demonstrate that secukinumab specifically binds to IL-17A and blocks its interaction with cell surface receptors, thereby suppressing the inflammatory response in psoriasis.

MDSCs are precursors of immature granulocytes, monocytes, and dendritic cells, and have been shown to mediate immunosuppression in psoriasis (Xu *et al*., 2024; Zhu & Cao, 2025; Zhu *et al*., 2024). In psoriasis, MDSCs promote the synthesis and release of IL-23 and IL-1β but fail to suppress T-cell proliferation, consequently exhibiting reduced expression of PD-1 and PD-L1 (Balderas-Miranda *et al*., 2026). Arg1 and iNOS are immunosuppressive factors whose upregulation in pathological environments facilitates the expansion of immunosuppressive immature myeloid cells, collectively termed MDSCs (Aintablian *et al*., 2023). Thus, Arg1 and iNOS are considered effector molecules of MDSCs. Zhang *et al*. demonstrated notable elevation in MDSCs in a psoriasis mouse model (Zhang *et al*., 2023), which aligns with the present study's findings of elevated MDSC proportions in the spleen of the psoriasis-like rat model. Additionally, aberrantly high Arg1 and iNOS in the target skin of model rats were noted, indicating a regulatory role for MDSCs in psoriasis progression. Furthermore, secukinumab treatment significantly reduced the proportion of MDSCs and decreased Arg1 and iNOS expression in the target skin of the rat model. MDSCs promote Th17 cell differentiation via IL-1β (Grassi *et al*., 2024). Although secukinumab does not directly inhibit IL-1β or IL-6 production or modulate Th17 cells, it specifically neutralizes IL-17A and disrupts the IL-17A-driven inflammatory circuit. This action suppresses the release of IL-1β and IL-6, inhibits Th17 cell activation, and ultimately modulates MDSCs' immunosuppressive function in psoriasis.

TRAF6 is a signaling adaptor and E3 ubiquitin ligase that regulates and activates NF-κB/MAPK signaling, thereby modulating immune functions (Xiao *et al*., 2023). Deficiency in TRAF6 expression can induce osteoporosis, thymic atrophy, absence of lymph nodes, and splenomegaly in mice (Petrova *et al*., 2022). TRAF6 also regulates the development of dendritic cells (Lu *et al*., 2023). Zhang *et al*. found that TRAF6 influences inflammatory responses mediated by NF-κB signaling axis and affects IL-17, IL-6, IFN-γ, and TNF-α, thereby participating in the regulation of psoriasis progression (Zhang *et al*., 2025). This study observed abnormally elevated TRAF6 expression in the target skin of a psoriasis-like rat model, which was reduced after secukinumab administration. Dysregulated TRAF6 signaling may attenuate NF-κB activity in the epidermis, allowing MAPK activation to dominate, potentially facilitating IL-17-driven responses and increasing susceptibility to psoriasis. As a key intracellular adaptor protein, TRAF6 plays a central role in signal transduction, including that mediated by the IL-17 receptor (Liu *et al*., 2023). Therefore, we speculate that by neutralizing IL-17A and blocking its signaling, secukinumab can inhibit the formation of the Act1/TRAF6 complex, thereby suppressing the activation of the TRAF6-mediated NF-κB/MAPK pathway and reducing inflammatory cytokines, ultimately downregulating the expression of TRAF6. However, its specific mechanism of action requires further experimental confirmation.

This study found that in a rat model of psoriasis-like dermatitis, the expression of TRAF6 in the skin was significantly elevated, and the proportion of MDSCs in the spleen as well as the levels of Arg1/iNOS in the skin were also markedly increased; in contrast, secukinumab treatment simultaneously decreased the expression of TRAF6, MDSCs and related effector molecules, accompanied by the alleviation of inflammation. These parallel changes suggested that TRAF6 and MDSCs might be jointly involved in the inflammatory regulatory network of psoriasis. The IL-17A signaling pathway has been confirmed to recruit TRAF6 via Act1 and activate the NF-κB/MAPK pathway. This study speculated that secukinumab might indirectly inhibit the activation and expression of TRAF6 by neutralizing IL-17A, thereby affecting the release of downstream inflammatory factors. As a key regulator of myeloid cell development and function (Xiao *et al*., 2023), the downregulation of TRAF6 might attenuate the expansion of MDSCs or the maintenance of their immunosuppressive phenotype, as reflected by the reduction in Arg1/iNOS and the improvement of imbalanced T-cell regulation.

However, this study still has certain limitations: (1) The small sample size, with only 5 rats per group, may affect the stability of the results; (2) It only reveals the correlations among TRAF6, MDSCs, and inflammatory parameters following secukinumab intervention, but does not directly establish a linear causal relationship among these three factors. For example, it remains unclear whether TRAF6 directly regulates the recruitment or function of MDSCs in psoriatic lesions; whether the changes in MDSCs are a result of TRAF6 downregulation or an independent effect following IL-17A blockade cannot be determined from the available data. (3) No exploration of the dose-response relationship was conducted. Nevertheless, the results of this study provided preliminary clues for the potential role of the IL-17A-TRAF6-MDSCs axis in psoriasis. Future studies were required to further verify the functional association of this

pathway through cell-specific genetic manipulation (such as TRAF6 knockout in myeloid cells), MDSC depletion/adoptive transfer experiments, or *in vitro* co-culture systems.

Conclusions: In summary, intravenously injecting secukinumab can improve the skin lesion symptoms in a rat model of psoriasis, reduce TRAF6 expression, decrease the proportion of MDSCs in the spleen, and stop the inflammation. These findings suggest a potential correlation between SEC treatment and the TRAF6-MDSC axis, but further mechanistic studies are needed to establish causality.

Authors' Contributions: Zijun Song, Jianqin Yu and Mengyun Zhou designed experiments; Zijun Song, Jianqin Yu and Mengyun Zhou analyzed data; Zijun Song, Jianqin Yu and Mengyun Zhou collected samples; Zijun Song, Jianqin Yu and Mengyun Zhou performed experiments; Zijun Song, Jianqin Yu and Mengyun Zhou wrote the manuscript. All authors agreed to publish this article.

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Animal rights statement: All animal experiments were approved by the Animal Ethics Committee of Hangzhou Normal University (Hangzhou, China) (No.2024148), in compliance with Chinese national guidelines for the care and use of animals.

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REFERENCES

Aintablian, A., S. Strozniak, M. Heuer, and M. B. Lutz (2023). M-MDSC in vitro generation from mouse bone marrow with IL-3 reveals high expression and functional activity of arginase 1. Front Immunol. 14: 1130600. https://doi.org/10.3389/fimmu.2023.1130600.

Balderas-Miranda, J. T., J. Torres-Ruiz, G. A. Guaracha-Basañez, B. Alcalá-Carmona, Y. Reyna-Juárez, M. J. Ostos-Prado, G. Juarez-Vega, N. R. Mejía-Domínguez, S. Méndez-Flores, V. Pascual Ramos, and D. Gómez-Martín (2026). Myeloid-derived suppressor cells and monocytes are biomarkers of the clinical phenotype and activity of psoriatic disease. Rheumatology (Oxford). 65(1): keaf465. https://doi.org/10.1093/rheumatology/keaf465

Chung, H. S., and H. S. Hwang, (2025). Therapeutic potential of phytochemical luteolin in restoring skin barrier by inhibiting antimicrobial peptides associated with TRAF6/TAK1/IKK/IκB in psoriasis-like HaCaT models. Food Sci Biotechnol. 34(12): 2909-2921. https://doi.org/10.1007/s10068-025-01894-z

Fischer, B., T. Kübelbeck, A. Kolb, J. Ringen, A. Waisman, M. Wittmann, S. Karbach, S. M. Kölsch, and D. Kramer (2023). IL-17A-driven psoriasis is critically dependent on IL-36 signaling. Front Immunol. 14: 1256133. https://doi.org/10.3389/fimmu.2023.1256133

Gargiulo, L., L. Ibba, P. Malagoli, A. Balato, F. Bardazzi, M. Burlando, C. G. Carrera, G. Damiani, P. Dapavo, V. Dini, F. M. Gaiani, G. Girolomoni, C. Guarneri, C. Lasagni, F. Loconsole, A. V. Marzano, M. Megna, S. R. Mercuri, M. Travaglini, A. Costanzo, and A. Narcisi (2024). Drug survival of IL-12/23, IL-17 and IL-23 inhibitors for moderate-to-severe plaque psoriasis: a retrospective multicenter real-world experience on 5932 treatment courses - IL PSO (Italian landscape psoriasis). Front Immunol. 14: 1341708. https://doi.org/10.3389/fimmu.2023.1341708

Grassi, G., S. Notari, S. Cicalini, R. Casetti, E. Cimini, V. Bordoni, R. Gagliardini, V. Mazzotta, A. Antinori, C. Agrati, and A. Sacchi, (2024). Brief Report: In cART-Treated HIV-Infected Patients, Immunologic Failure Is Associated With a High Myeloid-Derived Suppressor Cell Frequency. J Acquir Immune Defic Syndr. 95(2): 185-189. https://doi.org/10.1097/QAI.0000000000003335

Hseu, J. H., C. I. Chan, C. Vadivalagan, S. J. Chen, H. R. Yen, Y. C. Hseu, H. L. Yang, and P. Y. Wu, (2023). Tranexamic acid improves psoriasis-like skin inflammation: Evidence from in vivo and in vitro studies. Biomed Pharmacother. 166: 115307. https://doi.org/10.1016/j.biopha.2023.115307

Lasser, S. A., F. G. Ozbay Kurt, I. Arkhypov, J. Utikal, and V. Umansky (2024). Myeloid-derived suppressor cells in cancer and cancer therapy. Nat Rev Clin Oncol. 21(2): 147-164. https://doi.org/10.1038/s41571-023-00846-y

Liu, Y., Y. Meng, C. Zhou, J. Yan, C. Guo, and W. Dong (2023). Activation of the IL-17/TRAF6/NF-κB pathway is implicated in Aβ-induced neurotoxicity. BMC Neurosci. 24(1): 14. https://doi.org/10.1186/s12868-023-00782-8

Lu, Y., J. Chiang, R. Zhang, P. A. Roche, and R. J. Hodes (2023). TRAF6 and TRAF2/3 Binding Motifs in CD40 Differentially Regulate B Cell Function in T-Dependent Antibody Responses and Dendritic Cell Function in

Experimental Autoimmune Encephalomyelitis. J Immunol. 211(12): 1814-1822. https://doi.org/10.4049/jimmunol.2300607

Maravilla-Herrera, P., M. Merino, S. Alfonso Zamora, J. Balea Filgueiras, J. M.Carrascosa Carrillo, O. Delgado Sánchez, F. Dolz Sinisterra, A. García-Ruiz, P. Herranz Pinto, A. Manfredi, J. Martínez Olmos, P. Morales de Los Ríos Luna, L. Puig, S. Ros, and Á. Hidalgo-Vega (2023). The social value of a PASI 90 or PASI 100 response in patients with moderate-to-severe plaque psoriasis in Spain. Front Public Health. 11: 1000776. https://doi.org/10.3389/fpubh.2023.1000776

Marchlewicz, M., P. Sagan, M. Grabowska, M. Kiedrowicz, J. Kruk, K. Gill, M. Piasecka, and E. Duchnik (2024). The Role of Vitamin D3 Deficiency and Colonization of the Oral Mucosa by Candida Yeast-like Fungi in the Pathomechanism of Psoriasis. J Clin Med. 13(22): 6874. https://doi.org/10.3390/jcm13226874

Maronese, C. A., M. Valenti, C. Moltrasio, M. Romagnuolo, S. M. Ferrucci, M. Gilliet, A. Costanzo, and A. V. Marzano (2024). Paradoxical Psoriasis: An Updated Review of Clinical Features, Pathogenesis, and Treatment Options. J Invest Dermatol. 144(11): 2364-2376. https://doi.org/10.1016/j.jid.2024.05.015

Navarro-Compán, V., L. Puig, S. Vidal, J. Ramírez, M. Llamas-Velasco, C. Fernández-Carballido, R. Almodóvar, J. A. Pinto, E. Galíndez-Aguirregoikoa, P. Zarco, B. Joven, J. Gratacós, X. Juanola, R. Blanco, S. Arias-Santiago, J. Sanz Sanz, R. Queiro, and J. D. Cañete (2023). The paradigm of IL-23-independent production of IL-17F and IL-17A and their role in chronic inflammatory diseases. Front Immunol. 14: 1191782. https://doi.org/10.3389/fimmu.2023.1191782

Peng, L., W. Liu, Y. Cheng, L. Chen, and Z. Shen (2024). IL-17A/F double producing T cells, unstable Tregs and quiescent TRMs in clinically healed lesions are potential cellular candidates for recurrence of psoriasis. Clin Immunol. 266: 110328. https://doi.org/10.1016/j.clim.2024.110328

Petrova, T., K. Bennett, S. Nanda, S. Strickson, C. L. Scudamore, A. R. Prescott, and P. Cohen (2022). Why are the phenotypes of TRAF6 knock-in and TRAF6 knock-out mice so different?. PLoS One. 17(2): e0263151. https://doi.org/10.1371/journal.pone.0263151

Pixley, J.N., T. Schaetzle, and S.R. Feldman (2023). A Review of Topical Roflumilast for the Treatment of Plaque Psoriasis. Ann Pharmacother. 57(8): 966-969. https://doi.org/10.1177/10600280221137750

Roy, T., S. Banang-Mbeumi, S. T. Boateng, E. M. Ruiz, R. N. Chamcheu, L. Kang, J. A. King, A. L. Walker, B. M. Nagalo, K. G. Kousoulas, S. Esnault, S. Huang, and J. C. Chamcheu (2023). Dual targeting of mTOR/IL-17A and autophagy by fisetin alleviates psoriasis-like skin inflammation. Front Immunol. 13: 1075804. https://doi.org/10.3389/fimmu.2022.1075804

Ruscitti, P., M. Esposito, I. Di Cola, C. Pellegrini, A. De Berardinis, M. Mastrangelo, C. Gianneramo, A. Barile, M. C. Fargnoli, and P. Cipriani (2023). Cytokine profile characterization of naïve patients with psoriasis and psoriatic arthritis: implications for a pathogenic disease continuum. Front Immunol. 14: 1229516. https://doi.org/10.3389/fimmu.2023.1229516

Simopoulou, T., S. G. Tsiogkas, E. Zafiriou, and D. P. Bogdanos, (2023). Secukinumab, ixekizumab, bimekizumab and brodalumab for psoriasis and psoriatic arthritis. Drugs Today (Barc). 59(3): 135-167. https://doi.org/10.1358/dot.2023.59.3.3419557

Snyder, C. L., R. S. Gibson, M. L. Porter, and A. B. Kimball (2023). Secukinumab in the treatment of hidradenitis suppurativa. Immunotherapy. 15(17): 1449-1457. https://doi.org/10.2217/imt-2023-0103

Sugumaran, D., A. C. H. Yong, and J. Stanslas (2024). Advances in psoriasis research: From pathogenesis to therapeutics. Life Sci. 355: 122991. https://doi.org/10.1016/j.lfs.2024.122991

Wang, L., X. Liu, Y. Han, H. I. Tsai, Z. Dan, P. Yang, Z. Xu, F. Shu, C. He, J. E. Eriksson, H. Zhu, H. Chen, and F. Cheng (2024). TRAF6 enhances PD-L1 expression through YAP1-TFCP2 signaling in melanoma. Cancer Lett. 590: 216861. https://doi.org/10.1016/j.canlet.2024.216861

Wang, W., X. Xu, Y. Song, L. Lan, J. Wang, X. Xu, and Y. Du (2023). Nano transdermal system combining mitochondria-targeting cerium oxide nanoparticles with all-trans retinoic acid for psoriasis. Asian J Pharm Sci. 18(5): 100846. https://doi.org/10.1016/j.ajps.2023.100846

Xiao, J., Q. Han, Z. Yu, M. Liu, J. Sun, M. Wu, H. Yin, J. Fu, Y. Guo, L. Wang, and Y. Ma (2023). Morroniside Inhibits Inflammatory Bone Loss through the TRAF6-Mediated NF-κB/MAPK Signalling Pathway. Pharmaceuticals (Basel). 16(10): 1438. https://doi.org/10.3390/ph16101438

Xu, D., L. Tang, Y. Wang, J. Pan, and C. Su (2024). LC-MS-based rheumatoid arthritis serum metabolomics reveals the role of deoxyinosine in attenuating collagen-induced arthritis in mice. Heliyon. 10(10): e30903. https://doi.org/10.1016/j.heliyon.2024.e30903

Yuan, L. L., and C. Y. Cao (2023). Rehmannioside A Inhibits TRAF6/MAPK Pathway and Improves Psoriasis by Interfering with the Interaction of HaCaT Cells with IL-17A. Clin Cosmet Investig Dermatol. 16: 2585-2596. https://doi.org/10.2147/CCID.S430621

Yu, Y., W. Chen, B. Li, Z. Li, Y. Wang, Y. Mao, W. Fan, Y. Bai, H. Hu, Q. Zhen, and L. Sun (2024). Cutaneous Calcium/Calmodulin-Dependent Protein Kinase II-γ-Positive Sympathetic Nerves Secreting Norepinephrine Dictate Psoriasis. Adv Sci. 11(23): e2306772. https://doi.org/10.1002/advs.202306772

Zhang, J., Y. Zhang, Z. Yang, D. Cheng, H. Zhang, L. Wei, C. Liu, F. Yan, C. Li, G. Dong, C. Wang, D. Shi, and H. Xiong (2023). Inducible nitric oxide synthase-expressing myeloid-derived suppressor cells regulated by interleukin 35 contribute to the pathogenesis of psoriasis. Front Immunol. 14: 1091541. https://doi.org/10.3389/fimmu.2023.1091541

Zhang, W., G. Zhu, H. Sun, and C. Jiang (2025). NLRC3 affects the development of psoriasis by modulating the NF-κB signaling pathway mediated inflammatory response through its interaction with TRAF6. Immunol Lett. 272: 106949. https://doi.org/10.1016/j.imlet.2024.106949

Zhu, Y., and S. Cao (2025). Unraveling the Complexities of Myeloid-Derived Suppressor Cells in Inflammatory Bowel Disease. Int J Mol Sci. 26(7): 3291. https://doi.org/10.3390/ijms26073291

Zhu, Y., X. Chen, Y. Zou, L. Su, X. Yan, X. Zhu, Y. Hou, M. Liu, W. Jiang, C. Zou, X. Chen, and Z. Xu (2024). Ze-Qi-Tang formula inhibits MDSCs glycolysis through the down-regulation of p21/Hif1α/Glut1 signal in psoriatic-like mice. Phytomedicine. 130: 155544. https://doi.org/10.1016/j.phymed.2024.155544