Original Article

Dysfunction of regulatory T cells mediated by AKT-FOXO1 signaling pathway occurs during the development of psoriasis

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Abstract: Psoriasis is an immune-mediated skin disease with abnormal T cells. Regulatory T cells (Treg) are a kind of cell group with immunosuppressive effects. This study aimed to explore the role of Treg cells in the pathogenesis of psoriasis and its possible mechanism. Imiquimod induced psoriasis mice model was conducted. The skin lesions were evaluated according to the psoriasis area and severity index (PASI). Skin biopsies were taken for HE staining and immunohistochemical staining of IL-23, IL-17, IL-33 and TNF-α. CD4⁺CD25⁺ Treg cells were isolated. The proportions of Treg cells, cell proliferation, and immunosuppressive activity were analyzed by flow cytometry. The expression of AKT, Foxo1, pAKT, pFoxo1 protein, and the localization of Foxo1 protein in Treg cells were detected by western blot and immunofluorescence. The results showed that the psoriasis mice model was established successfully. There was no significant difference in the proportion of Treg cells between the two groups (P > 0.05). The cell proliferation abilities were decreased, and the immunosuppressive functions of Treg cells were weakened in the psoriatic group (P < 0.05). Western blot showed that pAKT and pFoxo1 levels of Treg cells were significantly increased in the psoriatic group (P < 0.05). Immunofluorescence showed that Foxo1 was mainly expressed in the nucleus of Treg cells in the control group, whereas expressed in the cytoplasm in the psoriasis group. Therefore, we concluded that the cell proliferation and immunosuppressive dysfunction of Treg cells mediated by AKT-FOXO1 signaling pathway may occurs during the development of psoriasis.

Keywords: Psoriasis, imiquimod, CD4⁺CD25⁺Foxp3⁺ Treg, CD4⁺ T cells, Akt-Foxo1

Introduction

Psoriasis is a common, chronic inflammatory cutaneous disorder characterized by abnormal differentiation and proliferation of keratinocytes and abnormal activation and infiltration of T lymphocytes [1, 2]. The etiology and pathogenesis of psoriasis are still unclear. Current studies [3-5] have found that psoriasis is an immune-mediated skin disease with abnormal T cells, which play an important role in the pathogenesis of this disease. Abnormal T cells enter the epidermis and dermis to produce cytokines, and interact with the inherent epidermal cells and endothelial cells of the skin, resulting in epidermal proliferation and skin thickening. Overactivation of Th1 and Th17 cells were recognized as a central link in psoriasis pathogenesis [6]. IL-23/Th17 [7] pathway plays a key role in the pathogenesis of psoriasis. IL-23 molecule secreted by dendritic cells can induce Th17 cells to secrete many cytokines such as IL-17 and IL-22. These cytokines can recruit neutrophile granulocyte and induce various inflammatory diseases such as psoriasis [8]. IL-17 is considered to be the most important cytokine in the pathogenesis of psoriasis [9, 10].

T regulatory cells (Treg) are a kind of cell group with immunosuppressive effects, which inhibit autoimmune T cell by cell-contact suppression or suppressive cytokines [11]. The primary phenotypes of Treg cells are CD4⁺CD25⁺Foxp3⁺ and Treg. Treg cells can exert their immunosuppression through many mechanisms, further maintaining immunotolerance [12]. Treg cells play an important role in autoimmune diseases [13]. Studies [14-16] have shown that Th17 and Treg cells have antagonistic effects on the bal-
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ance of the immune system. If the stability of Th17 and Treg is destroyed, it can induce abnormal or impaired immune response and lead to chronic inflammatory or immune diseases. Therefore, in addition to the over-activation of Th17, the weakening of negative regulation function of Treg cells may also be a key factor in persistent inflammation of psoriatic patients. At present, the research of Treg cells in psoriasis is still in the exploratory stage.

Forkhead box protein 1 (Foxo1) is a member of the Forkhead box (fox) family and encoded by the Foxo1 gene. It is primarily regulated through phosphorylation on multiple residues. Its transcriptional activity is dependent on its phosphorylation state. Foxo1 were highly expressed in Treg cells and participates in the maintenance of Treg mediated immune response. Foxo1 is also the downstream target gene of ALK pathway. The activation of AKT pathway can lead to the phosphorylation of Foxo1, which promotes Foxo1 transfer from nucleus to cytoplasm and loses its transcriptional function. AKT/Foxo1 play an important role in the development of Treg cells. Foxp3 (forkhead box P3), is also a member of the fox family involved in immune system responses. Foxp3 appears to function as a master regulator of the regulatory pathway in the development and function of regulatory T cells. Foxp3 is also a transcription factor and a Treg-specific marker that regulates Treg development.

Therefore, in order to clarify the role and mechanism of CD4+CD25+ and Foxp3+ Treg cells in the pathogenesis of psoriasis, the imiquimod-induced psoriasis-like mice model was used in our study to examine the number and function of CD4+CD25+ and Foxp3+ Treg cells in psoriasis, and to explore the regulatory role of Akt-Foxo1 signaling pathway on the function of Treg cells.

Materials and methods

Animals

Thirty SPF level of female BALB/c mice, 6 to 8 weeks old, weighing 18-20 g, were provided and fed by the experimental center of Affiliated Hospital of Hebei University of Engineering (animal certification number was SCXK 2011-0004). All animals were adaptive feeding 7 d before the experiment. Environmental temperature was controlled between 22 to 26°C. The humidity was controlled between 40 to 70%. Mice were permitted to eat and drink freely. A dose of 30 mg/kg was given by intraperitoneal injection of 3% sodium pentobarbital anesthesia. All the animals, reagents and treatment methods used in the experiments were approved by the animal experiment ethics committee of Affiliated Hospital of Hebei University of Engineering.

Reagents and instruments

Imiquimod cream (containing 5% IMQ) was purchased from Zhuhai federal pharmaceutical (China). Vaseline cream was bought from Unilever (USA). PEI transfection reagent, DMEM and cell culture medium additives, and DAB coloring solution, CFSE (carboxyfluorescein succinimidyl amino ester): 5- or 6-(N-succinimidyloxycarbonyl)-3',6'-0,0'-diacetylfluorescein were purchased from Sigma (USA). SDS-PAGE, BCA protein concentration assay kit and ECL developer were bought from Gibco (USA). HE staining reagent was bought from Jinqiao (Chinese). CD4 FITC, CD25 APC, Foxp3 PE and PE homologous control monoclonal antibody, fixative and film breaker were all purchased from Santa Cruz (USA). HRP labeled streptavidin and TMB were bought from TaKaRa (Japan). The monoclonal antibodies against AKT, Foxo1, pAKT, and pFoxo1 used in western blot were purchased from Abcam (USA). IL-17, IL-23, TNF-α and IL-33 antibodies, FITC labeled anti rabbit Ig G antibody, nuclear fluorescence staining DAPI re purchased from Sigma (USA). Lymphocyte separation fluid, CD3/CD28 monoclonal antibody, CD4+CD25+ Treg cell sorting kit, immunomagnetic bead sorter, MACS buffer, LD and MS MACS separation column were all purchased from Miltenyi Biotec (Germany).

Mice psoriasis model were induced by imiquimod

Thirty SPF level of female BALB/c mice were randomly divided into 2 groups, control group and psoriasis group. Back hair of the mice was shaved to form an exposed area about 2 × 3 cm². Imiquimod cream (containing IMQ 5%) was applied to the shaving area at a dose of 62.5 mg/only daily and the control group was given the same amount of Vaseline cream. This smear was applied for 8 days continuously. On day 8, all mice were sacrificed by cervical dislocation. Following this sacrifice, blood was obtained from the cardiac cavity. All animal welfare including efforts to minimize suffering
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and distress, use of analgesics or anesthetics, or special housing conditions were conducted according to the Care and Use Guide of Laboratory Animals and were approved by the animal experiment ethics committee of Affiliated Hospital of Hubei University of Engineering.

The skin lesions were evaluated according to the psoriasis area and severity index (PASI)

The skin administration sites were observed every day before giving the medicine, and scored according to the PASI scoring standard. Scoring criteria: 0 (none): no erythema scales on the surface; 1 (mild): some lesions were covered with scales, mainly fine scales, slightly higher than the normal skin surface, reddish; 2 (moderate): most lesions were completely or incompletely covered with scales, scales were patchy, moderately raised, the edge of the plaque was round or sloping, red; 3 (severe): almost all lesions covered with scales, scales thick layer, thick lesions, prominent protuberance, crimson; 4 (extremely severe): all lesions. Erythema (E), infiltration (I), scales (S) were scored 0-4 and the total scores were also added up. The average score of each group was calculated and the trend line of skin lesion integration was drawn to observe the changes of skin lesions in mice.

Skin lesions and the thickness of epidermis were measured by HE staining

After the mice were sacrificed, the skin of the smear area was cut according to the nine-grid method, immersed in 4% paraformaldehyde and fixed for 24 hours, dehydrated, paraffin embedded, sliced and stained with HE. Each specimen was randomly selected from 2 slices for observation and each slice was randomly selected for 3 positions for photography. The thickness of the epidermis was measured by the scale function of ImagePro Plus 6.

Detection of spleen index

The mice were weighed and the spleens were also weighed after execution. The spleen indexes (spleen mass/body mass) were calculated.

The levels of IL-23, IL-17, IL-33, and TNF-α were detected by Immunohistochemistry

Mice were euthanized at the 8 days time point. Blood was obtained from the cardiac cavity. 1.5 mL of peripheral blood was placed in a 50 mL aseptic centrifuge tube with 15 mL PBS mixed. The peripheral blood was slowly added into the 15 ml lymphocyte isolation solution along the tube wall and placed above the level of the lymphocyte isolation solution. The lymphocytes in the lymphocyte layer were collected by centrifugation at 2,000 r/min for 20 min and washed twice by PBS.

CD4⁺CD25⁺ T cells were isolated by magnetic cell sorting (MACS)

CD4⁺ T cells were isolated from PBMC using magnetic cell sorting. To isolate CD4⁺CD25⁺ and CD4⁺CD25⁻ T cells, purified CD4⁺ T cell populations were incubated with PE-labeled anti-CD25 Ab (Miltenyi Biotec) and anti-PE magnetic beads and were isolated by MACS separation column. CD4⁺CD25⁻ T cells were isolated by negative selection using anti-CD25 microbeads. The purity of CD4⁺, CD4⁺CD25⁺, and CD4⁺CD25⁻ T cell fractions were assessed by FACS®.

Flow cytometry analysis of Tregs

We adjusted PBMC to 1 × 10⁷/mL. 100 μL cell suspension was mixed with 10 μL CD4 FITC
Dysfunction of Treg cells occurs during the development of psoriasis and CD25 APC respectively, incubated at room temperature for 30 min in dark, washed and centrifuged with PBS, and then incubated with 1 μL fixation/permeabilization membrane breaker at room temperature for 40 min, washed twice with membrane breaking buffer, and added 10 μL Foxp3-PE and incubated in dark for 30 minutes, washed twice with membrane breaking buffer, suspended again with 500 μL PBS. The proportions of CD4+CD25+Foxp3+ Treg cells in CD4+ T cells were detected by flow cytometry.

The cell proliferation and immunosuppressive activity of Treg cells were analyzed by flow cytometry

Treg cells were isolated from the control group and the psoriasis group of mice. Teff cells were extracted from healthy nude mice. Treg cells and Teff cells were labeled with carboxyfluorescein diacetate succinimidyl ester (CFSE; Invitrogen; Thermo Fisher Scientific, Inc.) as follows: CFSE (4 μmol/l) was added to the target cell suspension at 37°C in 5% CO2 for 10 min. Then, the cells were washed and analyzed in a flow cytometer. CFSE-labeled target cells were resuspended in RPMI-1640 for further investigation. Treg cells and Teff cells were stimulated by CD3 antibody (1:1000, catalogue number: SAB4700041, Sigma, USA), CD28 (1:1000, catalogue number: SAB25-01674, Sigma, USA) antibody and IL-2 (1:500, catalogue number: SAB1403970, Sigma, USA). Proliferation of CFSE-labeled cells was assessed by flow cytometry. The proliferation index was calculated using ModFit software (Verity Software House).

Western blot analysis

The cultured Treg cells were collected in a centrifuge tube and then added to the cell lysate containing double enzyme inhibitors (protease and phosphatase). The proteins were fully cleaved and then collected. The total proteins were electrophoreitized with 10% SDS-PAGE and transferred to 0.22 micron PVDF membrane. The membrane was sealed at room temperature for 1 hour with TBST containing 5% skim milk and incubated overnight with monoclonal antibodies against AKT (1:1000, catalogue number: SAB4500796, Sigma, USA), pAKT (1:1000, catalogue number: SAB43-00410, Sigma, USA), Foxo1 (1:1000, catalogue number: SAB4300428, Sigma, USA), and pFoxo1 (1:1000, catalogue number: SAB45-02345, Sigma, USA). After 1 h was closed, dilute solution was added and incubated at 4°C for the night. Then, secondary antibody dilution solution was added and incubated for 1 h at room temperature. Finally, the immunoreactive protein bands were detected by a chemiluminescence imaging analysis system. The relative density of protein expression was quantified using Image J software 1.46.

Immunofluorescence

Treg cells were separated and inoculated in confocal culture dishes. The dishes were placed in 6-well plates and centrifuged for 1500 rpm for 5 min to make Treg cells adhere to the wall. 1 mL Fixation/permeabilization solution were added to the fixed solution, incubated at room temperature for 30 min, primary antibody, second antibody, DAPI staining was added in turn, stored at 4°C and protected from light, and laser confocal detection was carried out in 24 hours.

Statistical analysis

SPSS17.0 statistics software was employed to undergo statistical analysis. The measure data are represented by x±s. One-way ANOVA analysis of variance followed by Tukey’s multiple comparison test was used in multiple comparisons, and LSD-t test were adopted on comparison among groups. P < 0.05 were considered to be statistically significant. P values were designated as *P < 0.05, **P < 0.01 and ***P < 0.001.
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Results

Morphological changes of psoriasis induced by imiquimod in mice

The general picture showed that the typical appearance of psoriasis, such as erythema, scales and thickening of skin, appeared in the skin lesions of mice after 5% IMQ induction, and as time went on, the symptoms were more obvious, while no obvious skin lesions were found in the control group (Figure 1A). According to the PASI standard score, we drew a trend curve. After 2 days of administration, the mice in the psoriasis group began to show erythema and scales. After 3 days of administration, plaques began to appear. With the increase of administration times, the degree of erythema, scales and plaques gradually increased (Figure 1B).

Pathological changes of psoriasis induced by imiquimod in mice

HE staining showed that the epidermis of imiquimod-induced mice showed psoriasis-like changes, with incomplete keratinization, thin granular layer, thick spinous layer, and prolonged epidermal ridge (Figure 2A). The vertical thickness of the epidermis was detected by Image J software. The results showed that the epidermis of the psoriasis group was markedly thickened, which was about three times of the control group mice (Figure 2B, P < 0.01). The spleen index of the psoriasis group was significantly higher than that of the control group (Figure 2C, P < 0.05).

IL-23, IL-17, IL-33 and TNF-α were increased significantly in skin lesions of psoriasis mice

Immunohistochemical results showed that the levels of IL-23, IL-17, IL-33 and TNF-α in the dermis of the psoriasis group mice were all significantly higher than that of the control group (Figure 3, P < 0.05, P < 0.01, P < 0.01, P < 0.05), indicating that the dermis of the psoriasis group of mice were infiltrated by inflammatory cytokines.

The proportions of Treg cells in CD4+ T cells found no significant difference

Flow cytometry showed that there the proportion of CD4+CD25+Foxp3+ Treg cells in CD4+ T cells were not significantly different between psoriatic and control groups of mice (Figure 4). It was indicating that the proportion of Treg cells were not obvious abnormalities in psoriasis.

The deficiency of cell proliferation and immunosuppressive function of Treg cells

Flow cytometry showed that the proportions of CD4+CD25+Foxp3+ Treg cells in the second generation and above in the psoriatic group of mice were significantly lower than that of the
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Figure 2. Histologic changes of psoriasis-like skin lesions induced by imiquimod (n = 3). (A) The histologic changes (HE staining × 400) of psoriasis-like skin lesions induced by imiquimod of BALB/c mice in 8 days. (B) Comparison of epidermis thickness in skin lesions at day 8 of each groups and (C) Spleen index at day 8. *P < 0.05, **P < 0.01 versus the control groups.

Figure 3. The levels of IL-23, IL-17, IL-33, and TNF-α were detected by immunohistochemistry of BALB/c mice in 8 days (n = 3). The levels of IL-23, IL-17, IL-33 and TNF-α in the dermis of the psoriasis group of mice were significantly higher than those in the control group (× 100). *P < 0.05, **P < 0.01 versus the control groups.

control group after stimulation with CD3 antibody, CD28 antibody and IL-2 (Figure 5A, P < 0.01). CD3 antibody, CD28 antibody and IL-2 could significantly stimulate T effector cell (Teff) proliferation. Compared with the Teff group, Treg cells in the control group and the
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Figure 5. The cell proliferation and immunosuppressive activity of Treg cells were analyzed by flow cytometry (n = 3, t test). The cell proliferation ability was decreased, and the immunosuppressive function was weakened of Treg cells in the development of psoriatic. A. The proportions of more than secondary generation of CD4+CD25+Foxp3+ Treg cells in the psoriatic group of mice was significantly lower than that in the control group; *P < 0.05, **P < 0.01 versus the control groups. B. Compared with the Teff group, Treg cells of the control group and the psoriasis group could significantly inhibit Teff cell proliferation. However, compared with control, the inhibitory effect of Treg cells in the psoriasis group was significantly reduced. *P < 0.05 versus the control groups, **P < 0.01 versus the Teff groups.

Figure 6. The expression level of AKT, pAKT, Foxo1, and pFoxo1 protein of Treg cells was detected by western blotting. AKT-Foxo1 signaling pathway were activated in Treg cells of the psoriasis group (n = 3, t test). A. Protein blotting stripe. B. The relative of pFoxo1, Foxo1 and pAKT, AKT protein. *P < 0.05, **P < 0.01, P > 0.05 versus the control groups.

psoriasis group could significantly inhibit Teff cell proliferation (Figure 5B, P < 0.01). However, compared with the control group, the inhibitory effect of Treg cells in the psoriasis group were significantly reduced (Figure 5B, P < 0.05). There were indications that the proliferation abilities of Treg cell were decreased, and the immunosuppressive functions of Treg cell were weakened in the psoriatic.

AKT-Foxo1 signaling pathway in Treg cells

Western blot results showed that the levels of phosphorylated AKT (pAKT) and pFoxo1 in Treg cells of the psoriatic group of mice were significantly increased than that of the control group (Figure 6, P < 0.05, P < 0.01), but total AKT protein and total Foxo1 protein were not significantly changed (Figure 6, P > 0.05). Immunofluorescence showed that Foxo1 were...
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mainly expressed in the nucleus of Treg cells in the control group (Figure 7), whereas they were expressed in the cytoplasm in the psoriasis group (Figure 7). There were indications that the overactivation of AKT-Foxo1 pathway promotes Foxo1 migration from the nucleus to the cytoplasm in psoriasis.

Discussion

The etiological factors of psoriasis have not yet been entirely clear, but it is related with heredity, immune defect, and infection [18, 19]. Imiquimote is an agonist of Toll-like receptor (TLR)-7/8 [20]. In the psoriasis-like mice model, imiquimote binds to TLR7 in epidermal plasma-like dendritic cells and macrophages, causing the production of cytokine to mimic inflammatory changes in psoriasis. In our study, the psoriasis mice model was successfully established by imiquimod. The infiltration of IL-23, IL-17, IL-33 and TNF-α in the dermis of the psoriasis group was detected, which confirmed the pathogenic effect of inflammatory factors on psoriasis.

Treg cells are a cell group with immunosuppressive effects, which inhibit autoimmune T cell by cell-contact suppression or suppressive cytokines, contributing to the maintenance of immunological self-tolerance and immune homeostasis [21]. Teff cells were T effector cell, can promote immune inflammation. If the immunosuppressive function of Treg cell is normal, the Treg cell can inhibit Teff cell growth [22]. Current studies [23-25] have found that abnormal proportions and functions of Treg cells were found to exist in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type I diabetes and systemic sclerosis. In recent years, the roles of Treg cells in psoriasis were also gradually coming into our view. Sugiyama [26] et al. found that the number of CD4^+CD25^+Foxp3^+ Treg cells in the lesions and peripheral blood of psoriasis patients was significantly lower than that of normal people, and there was also a proliferation defect. Recent study also reported [27] that the immunosuppressive effect of Treg cells was also significantly reduced in psoriasis. Therefore, we speculate that the pathogenesis of psoriasis is not only abnormal activation of Th17 cells, but also closely related to the dysfunction of Treg cells. In our study, we confirm that the proportion of Treg cells are not significantly abnormal, Proliferation of Treg cells of control and psoriasis mice were detected with live cell dye, CFSE labeling, and flow cytometry. The results showed that the cell proliferation of Treg cells in psoriasis mice was decreased. In order to detect the immunosuppressive function of Treg cells in psoriasis mice, we detected the proportion of Treg cells by flow cytometry. The results showed that the cell proliferation of Treg cells in psoriasis mice was decreased. In order to detect the immunosuppressive function of Treg cells in psoriasis mice, we further detected the proportion of Treg cells by flow cytometry. The results showed that the cell proliferation of Treg cells in psoriasis mice was decreased.
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cells, we labeled Teff cell (extracted from healthy nude mice) with CFSE, and co-culture with Treg cells of control and psoriasis mice. If immunosuppressive function of Treg cell is normal, Treg cell can inhibit Teff cell growth. Proliferation of CFSE-labeled cells was assessed by flow cytometry. The proliferation index was calculated using ModFit software (Verity Software House). The results showed that the immunosuppressive function of Treg cells were weakened in psoriasis. Therefore, we concluded that the cell proliferation and immunosuppressive dysfunction of Treg cells may occur during the development of psoriasis.

FOX (Forkhead box) are a family of transcription factors that play important roles in regulating the expression of genes involved in cell growth, proliferation, differentiation, and longevity. FOX proteins also have pioneering transcription activity by being able to bind condensed chromatin during cell differentiation processes [28]. The Foxo family includes Foxo1, Foxo3, Foxo4 and Foxo6 [29]. Treg cell display stringent dependence to the transcription factor Foxp3 [30]. Foxp3 is considered to be a key transcription factor and specific marker of Treg cells. Foxp1, a member of Foxp3 family, is essential for sustaining optimal expression of Foxp3 specifically in Treg cells. Foxo1 [31] monomer can directly bind to the transcription initiation region of target gene DNA, mainly the 5'-TTGTTTAC-3' structure sequence, and regulate gene transcription. Subcellular localization of Foxo1 is the key factor affecting its transcriptional activity, and protein modification is the main element affecting its subcellular localization. It is primarily regulated through phosphorylation on multiple residues; its transcriptional activity is dependent on its phosphorylation state [32]. Foxo1 is the downstream target gene of ALK pathway. The activation of AKT pathway can leads to the phosphorylation of Foxo1 [33], the affinity of phosphorylated FoxOs to DNA were decreased, cause nuclear exclusion, the affinity to chaperone 14-3-3 protein in cytoplasm were increased, which promotes Foxo1 transfer from nucleus to cytoplasm and loses its transcriptional function [34, 35]. Current research [36] confirmed that, during the development of Treg cells, Foxo1 can directly bind to the transcription promoter region of Foxp3 and initiate the transcription of Foxp3. The activation of AKT pathway can phosphorylate Foxo1, promoting Foxo1 migration from nucleus to cytoplasm. In cytoplasm, Foxo1 can lose transcriptional functions [37, 38]. In our study, we found that AKT-Foxo1 was activated in Treg cells of the psoriatic group. Foxo1 was mainly expressed in cytoplasm in Treg cells of the psoriatic group, whereas was expressed in the nucleus of the control group. We speculate that the overactivation of AKT-Foxo1 pathway promotes Foxo1 migration from nucleus to cytoplasm and loses its transcriptional function contributing to dysfunction of the Treg cell. Maybe it was one of the efficiency mechanisms.

Conclusion

We concluded that the cell proliferation and immunosuppressive dysfunction of Treg cells mediated by AKT-FOXO1. Signaling pathway may occur during the development of psoriasis. However, whether Treg cells contribute to the pathogenesis of psoriasis. Further experiments are needed.

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Disclosure of conflict of interest

None.

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