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ORIGINAL ARTICLE

Knockdown of Bcl-3 alleviates psoriasis and dyslipidemia comorbidity by regulating Akt pathway

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Abstract
Background: Psoriasis is considered as an inflammatory skin disease accompanied by dyslipidemia comorbidity. B-cell leukemia-3 (Bcl-3) belongs to IκB (inhibitor of nuclear factor kappa B [NF-κB]) family, and regulates inflammatory response through associating with NF-κB. The role of Bcl-3 in psoriasis was investigated in this study.
Methods: Apolipoprotein E (ApoE)-deficient mice were treated with imiquimod to induce psoriasis and dyslipidemia. Mice were injected intradermally in the back with lentiviral particles encoding Bcl-3 small hairpin RNA (shRNA). Hematoxylin and eosin were used to detect pathological characteristics. The blood lipid levels were determined by automatic biochemical analyzer, and inflammation was assessed by enzyme-linked-immunosorbent serologic assay and real-time quantitative reverse transcription polymerase chain reaction.
Results: Bcl-3 was elevated in imiquimod-induced ApoE-deficient mice. Injection with lentiviral particles encoding Bcl-3 shRNA reduced Psoriasis area and severity index (PASI) score in ApoE-deficient psoriatic mice. Knockdown of Bcl-3 also ameliorated imiquimod-induced psoriasiform skin lesions in ApoE-deficient mice. Moreover, loss of Bcl-3 enhanced expression of loricrin, an epidermal barrier protein, reduced expression of proliferating cell nuclear antigen (PCNA) and lectin-like oxidized LDL (oxLDL) receptor-1 (LOX-1) in imiquimod-induced ApoE-deficient mice. The enhanced levels of blood lipid in ApoE-deficient mice were attenuated by silencing of Bcl-3 with increase of high-density lipoprotein, and reduction of total cholesterol, triglycerides, and low-density lipoprotein cholesterol. Knockdown of Bcl-3 attenuated imiquimod-induced decrease of transforming growth factor beta (TGF-β), and increase of Interleukin (IL)-17A, IL-23, IL-6, and tumor necrosis factor-α (TNF-α) in ApoE-deficient mice. Protein expression of phospho-Akt (p-Akt) and p-GSK3β in ApoE-deficient psoriatic mice was decreased by silencing of Bcl-3.

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Conclusion: Loss of Bcl-3 exerted anti-inflammatory effect on psoriasis and dyslipidemia comorbidity through inactivation of Akt/GSK3β pathway.

Introduction

Psoriasis is an immune-mediated, long-term multifactorial skin disease, which affects about 2–3% of adults worldwide.[1] Psoriasis is caused by diverse factors, such as overproliferation and abnormal differentiation of keratinocytes, and infiltration of leukocytes into the dermis and epidermis.[2] The activated and infiltrated immune cells interact with hyperproliferative keratinocytes to induce epidermal thickening and psoriatic lesions.[2] Severity of psoriasis stimulates systemic inflammation, and induces endothelial cell dysfunction and insulin resistance, thus contributing to serious complications, such as autoimmune diseases, depression, sleep apnea, obesity, and psoriatic arthritis.[2] Therefore, anti-inflammatory strategies have been considered to be effective therapeutic tools for the treatment of psoriasis and psoriasis-associated diseases.[3]

Clinical and epidemiological data have established that the level of high-density lipoprotein cholesterol (HDL) was decreased, while the levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) were increased in psoriatic patients.[4] Lipid metabolism was also abnormally regulated in skin lesions of psoriatic patients.[5] Dyslipidemia comorbidity is a common complication of psoriasis, which is associated with metabolic syndrome, such as atherosclerosis, and cardiovascular mortality.[6] Amelioration of dyslipidemia in psoriasis patients is of great significance to reduce the risk of severe metabolic syndrome. Previous study has demonstrated that imiquimod-induced apolipoprotein E (ApoE)-deficient mice exhibited dyslipidemia through elevation of serum lipid levels.[6] Moreover, pathological features of psoriasis, such as infiltration of inflammatory cells, parakeratosis, and hyperplasia, were also observed in imiquimod-induced ApoE-deficient mice.[6] Therefore, imiquimod was used for establishing animal model of psoriasis with dyslipidemia in ApoE-deficient mice.

Proteins involved in Bcl family exert either pro-apoptotic or anti-apoptotic effects on keratinocyte during the development of psoriasis.[7] Dysregulated keratinocyte apoptosis has been demonstrated as associated with epidermal thickening during the development of inflammatory and hyperproliferative skin disorders.[8] B-cell leukemia-3 (Bcl-3) belongs to the Bcl family, regulating the expression of pro-survival genes in cutaneous T-cell lymphoma.[9] Moreover, Bcl-3 also binds to the promoter regions of inflammatory factors, and exhibits immunosuppressive effect in cutaneous T-cell lymphoma.[9] Bcl-3 functioned as an atypical inhibitor of NF-κB to attenuate inflammation in biliary and pancreatic tissues.[10] Bcl-3 was elevated in epidermal keratinocytes from the psoriatic skin, and overexpression of Bcl-3 increased the expression of psoriasis-related genes.[11] Furthermore, Bcl-3 was involved in dyslipidemia.[12] However, the role of Bcl-3 in psoriasis with dyslipidemia remains unclear.

In this study, effects of Bcl-3 on lipid metabolism and inflammation in imiquimod-induced ApoE-deficient mice were investigated.

Materials and Methods

Animal model

A total of six male C57BL/6J mice and 18 ApoE-deficient C57BL/6J mice (8–10-week old) were acquired from Beijing Vital River Experimental Animal Technology Co. Ltd. (Beijing, China). These experiments were approved by Animal Welfare Ethics Committee of Zhejiang Animal Experiment Center Laboratory, and were in accordance with the National Institutes of Health Laboratory Animal Care and Use Guidelines. Male C57BL/6J mice, which were considered as control group, received vaseline on the dorsal skin for 5 days consecutively. ApoE-deficient mice were divided into three groups: ApoE-deficient (n = 6); ApoE-deficient with short hairpin negative control (sh-NC) (n = 6), and ApoE-deficient with sh-Bcl-3 (n = 6). Short hairpin RNA (shRNA) targeting Bcl-3 (sh-Bcl-3) and sh-NC (Shanghai Sunbio, Shanghai, China) were constructed into pMagic 5.1 lentiviral vector. The lentiviral vectors were then transfected into 293T cells with pHelper vector 2.0 and pHelper vector 1.0 (Shanghai Sunbio) for 48 h. Lentiviral particles in the supernatants of cultured 293T cells were collected, and injected intradermally in the back of ApoE-deficient mice. Then, ApoE-deficient mice received 5% imiquimod (62.5 mg; Sigma-Aldrich, St. Louis, MO, USA) on the dorsal skin for five days as described by Xie et al.[13] Skin lesions in mice were observed and photographed every day. Psoriasis area and severity index (PASI) score was recorded with following standards: 0: for mice without scaling, infiltration, and erythema; 2: for mice with mild scaling, infiltration, and erythema; 4: for mice with moderate scaling, infiltration, and erythema; and 6: for mice with severe scaling, infiltration, and erythema.

Histology

The skin of ApoE-deficient mice were isolated and fixed in 4% formaldehyde. Tissues were embedded in paraffin, and sliced into 4-μm thick sections. The sections were then deparaffinized and rehydrated. Hematoxylin and eosin (H&E; Sigma-Aldrich) were used to stain these sections, and

histopathological changes were photographed under microscope (Olympus, Tokyo, Japan) as described by Xie et al.[13]

Determination of lipids level and inflammatory cytokines

Blood samples were acquired from mice and centrifuged at 1000 g for 15 min to collect serum samples. Serum levels of TC, triglycerides (TG), LDL, and HDL were measured by automatic biochemical analyzer (Hitachi, Tokyo, Japan).

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR)

The skin of experimental mice were lysed using TRIzol kit (Life Technologies, Carlsbad, CA, USA), and isolated RNAs were synthesized into complementary DNA (cDNAs). The cDNA was subjected to SYBR® Premix Ex Taq™ (Takara, Dalian, Liaoning, China) to detect messenger RNA (mRNA) expression of IL-17A, IL-23, IL-6, tumor necrosis factor-α (TNF-α), and transforming growth factor beta (TGF-β). The following primers were used in this study: IL-17A (forward: 5'-CAGACTACCTCAACCGTTCCAC-3' and reverse: 5'-TCCAGCTTTCCCTCCGCATTGA-3'), IL-23 (forward: 5'-GGACAACAGTCAGTTCTGCTT-3' and reverse: 5'-CACAGGGCTATCAGGGAGC-3'), IL-6 (forward: 5'-ACAGC CACTCACCTCTTCAG-3' and reverse: 5'-CCATCTTTTTCAGC CATCTTT-3'), TNF-α (forward: 5'-CCCGAGTGACAAGCCT GTAG-3' and reverse: 5'-GATGGCAGAGAGGAGGTTGAC-3'), TGF-β (forward: 5'-CGACTACTACGCCAAGGA-3' and reverse: 5'-GAGAGCAACACGGGTTCA-3'). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (forward: 5'-ACCTTCACTCCTCCAT CTT-3', reverse: 5'-AGGTCACAGACACGGTTG-3') was used as an internal control.

Western blot analysis

Skin tissues were lysed in RIPA buffer (Beyotime, Beijing, China), and the isolated protein samples were segregated using SDS-PAGE. Samples were transferred onto nitrocellulose membranes, and the membranes were blocked with 5% dry milk. The membranes were incubated with primary antibodies, including anti-Bcl-3 and anti-LaminA (1:2000), anti-PCNA and anti-loricrin (1:2500), anti-LOX-1 and anti-GAPDH (1:3000), anti-p-Akt and anti-Akt (1:3500), and anti-p-GSK3β and anti-GSK3β (1:4000). The membranes were incubated with secondary antibodies (1:4500), and subjected to chemiluminescence reagent kit (Beyotime) according to Xie et al.[13] All proteins were purchased from Abcam (Cambridge, MA, USA).

Statistical analysis

All the data were expressed as mean ± standard error of mean (SEM) and analyzed by Student's *t*-test or one-way analysis of variance (ANOVA); $P < 0.05$ was considered as statistically significant.

Results

Knockdown of Bcl-3 ameliorated psoriasiform skin lesions in imiquimod-induced ApoE-deficient mice

In order to induce animal model of psoriasis and dyslipidemia, ApoE-deficient mice were treated with imiquimod. Protein expression of Bcl-3 was elevated in ApoE-deficient psoriatic mice (Figure 1A). Imiquimod increased PASI score (Figure 1B) with hypertrophy and infiltration, large number of patchy scales, and a small amount of bleeding in the dorsal skin (Figure 1C). ApoE-deficient psoriatic mice were injected with lentiviral particles of sh-Bcl-3, and the protein expression of Bcl-3 was down-regulated post-sh-Bcl-3 injection (Figure 1A). Moreover, sh-Bcl-3 injection reduced PASI score (Figure 1B) and ameliorated skin erythema and scales in psoriatic mice (Figure 1C), suggesting the protective effect of silencing of Bcl-3 against psoriasis.

Knockdown of Bcl-3 ameliorated pathological characteristics of skin lesions in imiquimod-induced ApoE-deficient mice

Imiquimod also induced parakeratosis and keratinocyte hyperplasia in the epidermis of mice (Figure 2A). Infiltrations of inflammatory cells were observed in the dermis and epidermis of imiquimod-induced ApoE-deficient mice (Figure 2A). However, injection of sh-Bcl-3 reduced parakeratosis, suppressed inflammatory infiltration, and reduced epidermal thickness (Figure 2A). Then the proteins involved in psoriasis were evaluated. Results demonstrated that imiquimod decreased the protein expression of loricrin, an epidermal barrier protein, and increased the expression of PCNA and LOX-1 in the skin of mice (Figure 2B). Knockdown of Bcl-3 enhanced loricrin, and reduced PCNA and LOX-1 expression in imiquimod-induced ApoE-deficient mice (Figure 2B) to improve pathological characteristics of psoriasis.

Knockdown of Bcl-3 regulated lipid metabolism in imiquimod-induced ApoE-deficient mice

Level of HDL was down-regulated, while levels of TC, TG, and LDL were up-regulated in ApoE-deficient mice (Figure 3). However, silencing of Bcl-3 increased serum level of HDL, decreased TC, TG, and LDL in imiquimod-induced ApoE-deficient mice (Figure 3) to attenuate dyslipidemia comorbidity.

Knockdown of Bcl-3 ameliorated inflammatory response in imiquimod-induced ApoE-deficient mice

Imiquimod promoted down-regulation of TGF-β, up-regulation of IL-17A, IL-23, IL-6, and TNF-α in mice (Figure 4). Knockdown of Bcl-3 enhanced mRNA expression of TGF-β, reduced the expression of IL-17A, IL-23, IL-6, and

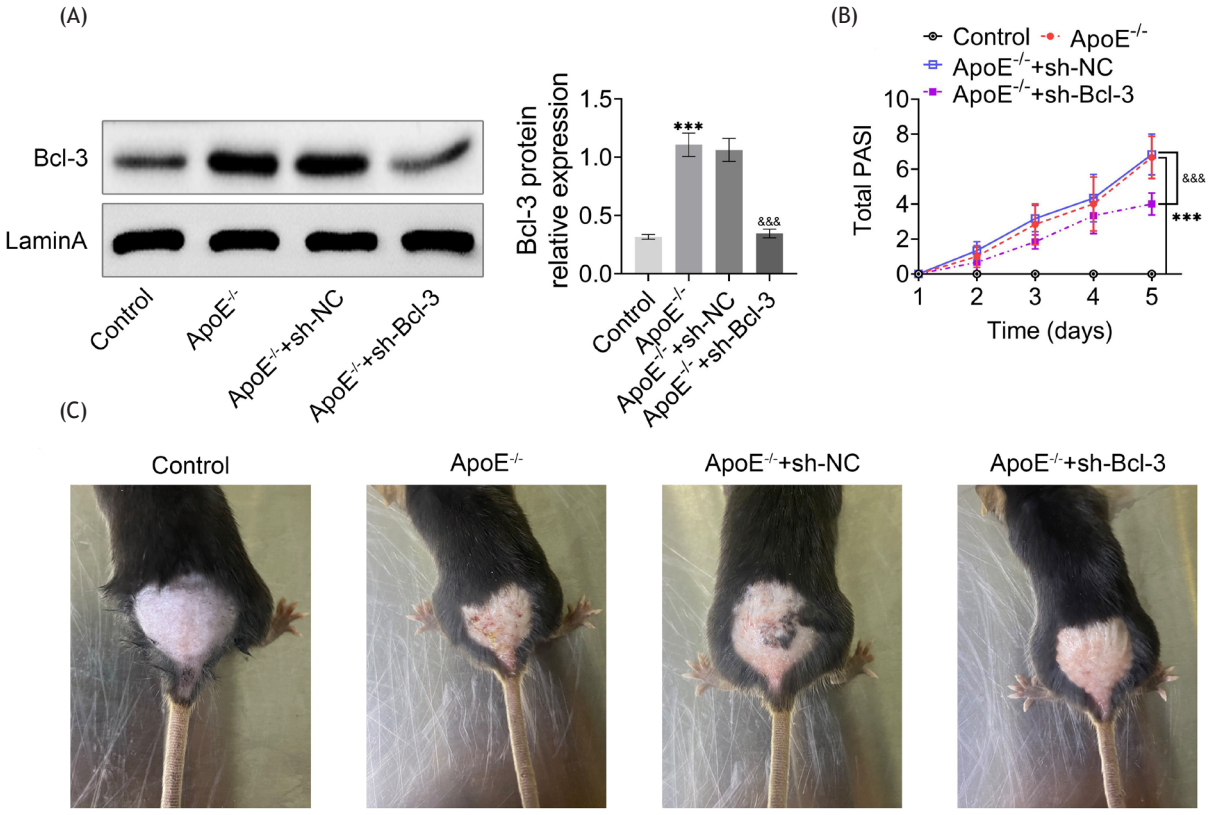

Figure 1 Knockdown of Bcl-3-ameliorated psoriasiform skin lesions in imiquimod-induced ApoE-deficient mice. (A) Expression of Bcl-3 was elevated in imiquimod-induced ApoE-deficient mice, while sh-Bcl-3 injection reduced Bcl-3 expression. (B) Knockdown of Bcl-3 attenuated imiquimod-induced increase of PASI score in ApoE-deficient mice. (C) Knockdown of Bcl-3 ameliorated skin erythema and scales in psoriatic mice. ***vs. control, $P < 0.001$. &&&vs. sh-NC, $P < 0.001$.

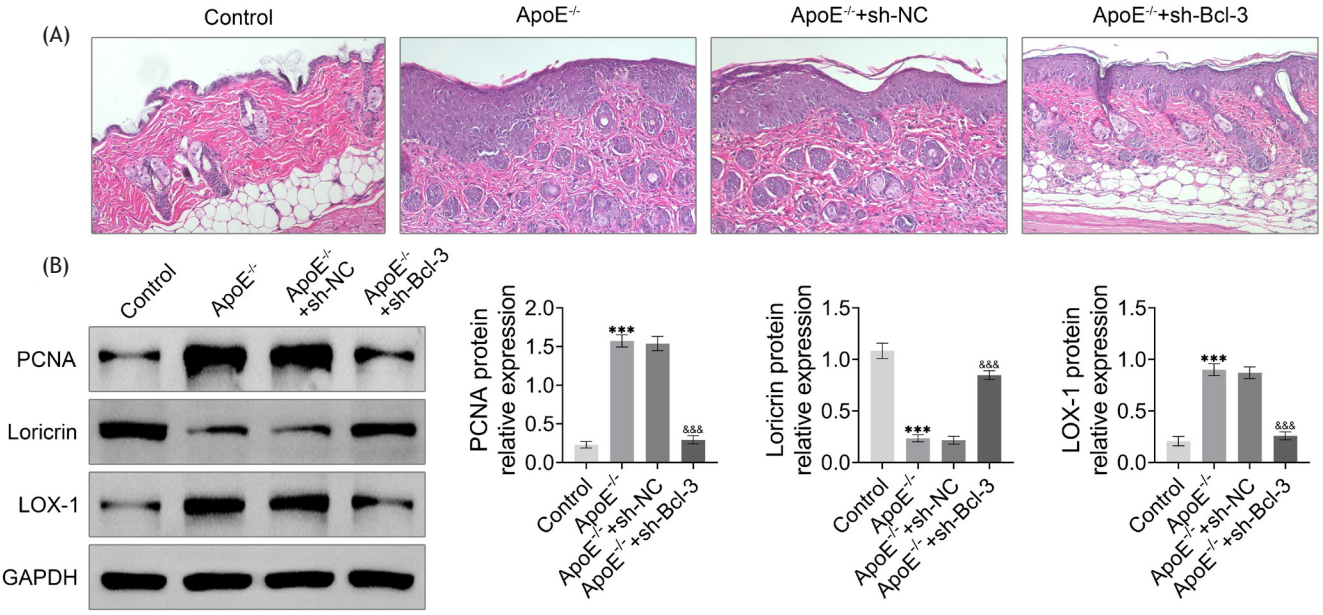

Figure 2 Knockdown of Bcl-3 ameliorated pathological characteristics of skin lesions in imiquimod-induced ApoE-deficient mice. (A) Knockdown of Bcl-3 reduced parakeratosis, suppressed inflammatory infiltration, and decreased the epidermal thickness in imiquimod-induced ApoE-deficient mice. (B) Knockdown of Bcl-3 enhanced loricrin expression, and reduced PCNA and LOX-1 expression in imiquimod-induced ApoE-deficient mice. ***vs. control, $P < 0.001$. &&&vs. sh-NC, $P < 0.001$.

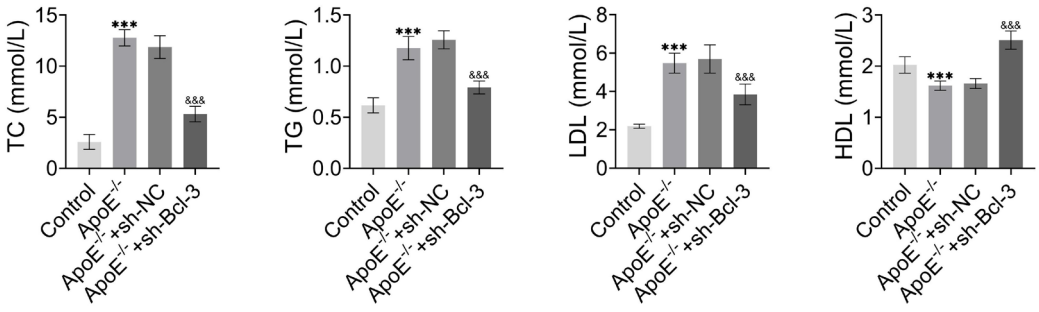

Figure 3 Knockdown of Bcl-3 regulated lipid metabolism in imiquimod-induced ApoE-deficient mice. Silencing of Bcl-3 increased serum level of HDL, decreased TC, TG, and LDL levels in imiquimod-induced ApoE-deficient mice. ***vs. control, $P < 0.001$. &&&vs. sh-NC, $P < 0.001$.

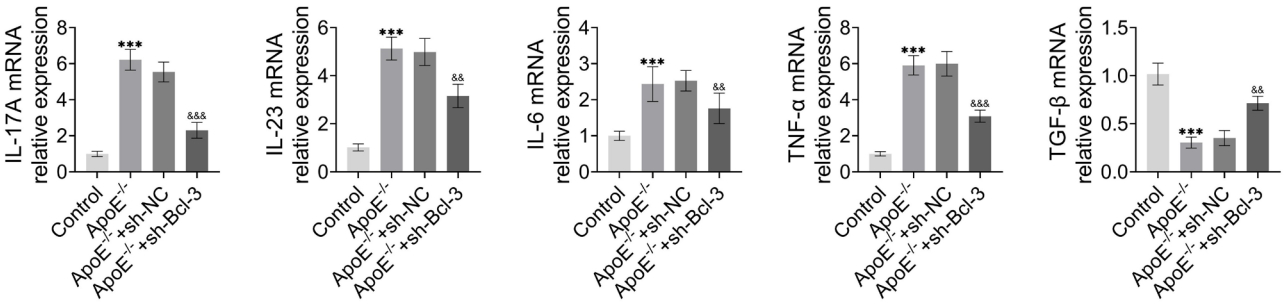

Figure 4 Knockdown of Bcl-3 ameliorated inflammatory response in imiquimod-induced ApoE-deficient mice. Knockdown of Bcl-3 enhanced mRNA expression of TGF-β, and reduced IL-17A, IL-23, IL-6, and TNF-α expression in skin tissues of imiquimod-induced ApoE-deficient mice. ***vs. control, $P < 0.001$. &&, &&&vs. sh-NC, $P < 0.01$, $P < 0.001$.

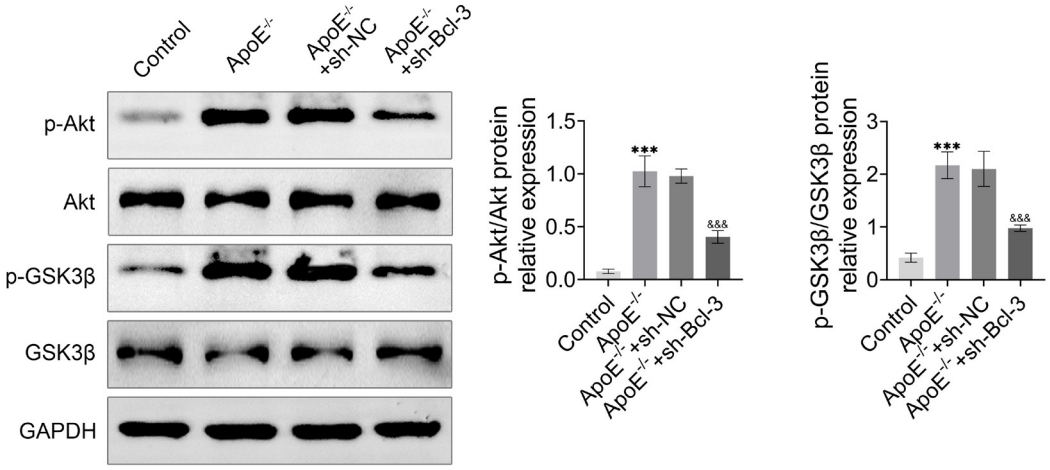

Figure 5 Knockdown of Bcl-3 mediated Akt/GSK3β signaling in imiquimod-induced ApoE-deficient mice. Knockdown of Bcl-3 reduced p-Akt and p-GSK3β expression in imiquimod-induced ApoE-deficient mice. ***vs. control, $P < 0.001$. &&&vs. sh-NC, $P < 0.001$.

TNF-α in skin tissues (Figure 4), thus demonstrating the anti-inflammatory effect of knocking Bcl-3 against psoriasis.

Knockdown of Bcl-3 mediated Akt/GSK3β signaling in imiquimod-induced ApoE-deficient mice

Protein expression of p-Akt and p-GSK3β were up-regulated in the skin of imiquimod-induced ApoE-deficient mice (Figure 5). Interference of Bcl-3 reduced p-Akt and p-GSK3β expression (Figure 5), revealing that knockdown of Bcl-3 suppressed activation of Akt/GSK3β in imiquimod-induced ApoE-deficient mice.

Discussion

As an inflammatory disease, psoriasis could also induce systemic inflammation and contribute to the development of

metabolic disorders, such as dyslipidemia.[6] Proteins in the B-cell leukemia (Bcl) family, B-cell lymphoma-extra (Bcl-X), and Bcl-2-associated X (Bax) were elevated in psoriatic epidermis.[14] Bcl-2 was down-regulated in psoriatic epidermis, which was associated with apoptosis of psoriatic keratinocytes.[14] This study found that Bcl-3 was also involved in psoriasis, and knockdown of Bcl-3 reduced inflammatory response and ameliorated psoriasiform skin lesions in psoriatic mice. Moreover, overexpression of Bcl-3 reduced export and hydrolysis of fatty acids, enhanced lipogenesis and uptake to induce hepatic steatosis in mice.[15] This study also found that silencing of Bcl-3 enhanced serum level of HDL, reduced TC, TG, and LDL levels to alleviate dyslipidemia in psoriatic mice.

In this study, ApoE-deficient mice were treated with imiquimod, and the psoriasiform skin lesions and elevation of serum lipid levels confirmed the successful establishment of psoriasis model with dyslipidemia. Knockdown of Bcl-3 attenuated dyslipidemia through up-regulation of HDL, down-regulation of TC, TG, and LDL. LOX-1, a receptor of oxidized LDL, was increased in the epidermis of psoriatic mice, which was associated with dyslipidemia.[16] Knockdown of Bcl-3 attenuated imiquimod-induced up-regulation of LOX-3 in ApoE-deficient mice. Moreover, the pathological characteristics of skin lesions in imiquimod-induced ApoE-deficient mice were also alleviated by silencing of Bcl-3. PCNA, important for proliferation of keratinocytes, was increased in imiquimod-induced mice.[17] Loricrin, an epidermal barrier protein, was also elevated in psoriatic mice.[18] Silencing of Bcl-3 reduced expression of PCNA and loricrin in imiquimod-induced ApoE-deficient mice to inhibit proliferation of keratinocytes and ameliorate epidermal barrier.

Th17 cells and Th17-associated cytokines, IL-23 and IL-17A, were implicated in the pathogenesis of psoriasis.[19] Th1, Th2, and Th17 cells also produced pro-inflammatory factors, including TNF-α and IL-6, to form complex network with keratinocytes and dendritic cells, and contributed to the development of psoriasis.[20] Furthermore, the inflammatory cytokines regulated biosynthesis of fatty acids and cholesterol, and dyslipidemia with up-regulation of intracellular cholesterol, and also stimulated production of IL-17A, TNF-α, and IL-6.[21] IL-23–IL-17 axis was considered to be a potential target for treatment of psoriasis with dyslipidemia.[13] Moreover, TGF-β1 was found to be a growth inhibitor for keratinocytes, and down-regulation of TGF-β potentiated hyperproliferation of keratinocytes in the epidermis of psoriasis mice.[22] Bcl-3 in keratinocytes regulated secretion of chemokines, modulated recruitment of neutrophils, and regulated inflammation in mice model of contact hypersensitivity.[23] Bcl-3 regulated expression of TNF-α and IL-6 in high-fat/high-carbohydrate diet-induced mice,[15] IL22 and IL-17A-induced interaction, and translocation of Bcl-3 and p50 into nucleus to regulate genes involved in psoriasis.[11] Furthermore, deletion of Bcl-3 inhibited pulmonary metastasis of breast cancer through promotion of TGF-β signaling.[24] In this study, knockdown of Bcl-3 enhanced TGF-β expression, reduced IL-17A, IL-23, IL-6, and TNF-α expression in imiquimod-induced ApoE-deficient mice, suggesting that Bcl-3 might exert an anti-inflammatory effect against psoriasis with dyslipidemia through mediation of IL-23–IL-17 axis.

Akt/GSK3β signaling plays a critical role in cell apoptosis, proliferation, and survival.[25] Activation of PI3K/Akt/mechanistic target of rapamycin (mTOR) up-regulated expression of IL-17A, TNF-α, and IL-1β, and contributed to the development of psoriasis.[26] Inhibition of PI3K/Akt/mTOR attenuated psoriasis[27] and psoriasis with dyslipidemia.[13] Bcl-3 promoted activation of Akt signaling to stimulate colorectal tumorigenesis.[28] Akt could also phosphorylate Bcl-3 and induce nuclear localization of Bcl-3;[29] inhibition of PI3K reduced expression of Bcl-3.[30] Results of this study demonstrated that knockdown of Bcl-3 reduced expression of p-Akt and p-GSK3β to ameliorate imiquimod-induced ApoE-deficient mice.

Conclusion

Silencing of Bcl-3 improved psoriasis skin lesions, inhibited inflammation, and regulated lipid metabolism in imiquimod-induced ApoE-deficient mice through inactivation of Akt/GSK3β signaling. Bcl-3 might be a novel target for the treatment of psoriasis with dyslipidemia. However, the effect of Bcl-3 on *in vitro* psoriatic keratinocyte model should be investigated in the future research.

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Competing Interests

The authors stated that there was no conflict of interest to declare.

Data Availability

The authors declare that all data supporting the findings of this study are available in the paper, and any raw data can be obtained from the corresponding author upon request.

Author Contributions

Wei Li designed the experiments, and Wei Yang and Can Yang carried out the same. All authors analyzed and interpreted the data, and prepared the manuscript with contributions from all coauthors.

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