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GLP-1 receptor agonist impairs keratinocytes inflammatory signals by activating AMPK☆

Jing Yang, Zongming Wang*, Xilin Zhang

Department of Dermatology and Venerology , Chongqing Three Gorges Central Hospital, ChongQing 404100, China

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ABSTRACT

Purpose: Liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, is an antidiabetic drug. It has been shown to improve the Psoriasis Area and Severity Index (PASI) in patients with type 2 diabetes and psoriasis in clinical practice, but the mechanism remains somewhat unclear. We used lipopolysaccharides (LPS) to induce inflammatory response in keratinocytes and explore the mechanism.

Methods: The HaCat cells were incubated with LPS for 16 h and then were treated with liraglutide for 30 min. Cell viability was testing by CCK-8 assay. GLP-1Rs and intracellular signaling pathways were identified by Western blot. The migration of macrophage was detecting by trans-well assay.

Results: Liraglutide decreased cell viability in the HaCat cells. Liraglutide restrained the migration of macrophage to the HaCat cells. LPS elevated not only the protein abundance of phospho-IKKα/β S176/S180, phospho-NF-κB p65, phospho-JAK2, phospho-STAT3 and SOCS3, but also the levels of TNF-α and IL-6 in the HaCat cells. These effects of LPS were reversed by liraglutide. In addition, liraglutide increased phosphorylation of AMPK. The AMPK inhibitor Compound (CC) impaired liraglutide-inhibited p-NF-κB p65 and p-STAT3.

Conclusions: GLP-1 impaired keratinocytes inflammatory signals by activating AMPK and restrained macrophage migration.

1. Introduction

Psoriasis is a common, chronic and non-infectious skin disease affecting approximately 125 million people globally, which has a long disease course (CEM et al., 2017). The hyper-proliferation and abnormal differentiation of epidermal keratinocytes, chronic inflammatory reaction and T-cell mediated disorder are the major pathological feature of psoriasis, which is characterized by erythema and scales. In addition, with unstable and economic pressure, more and more psoriasis patients are suffering from the physical and mental disease (Nestle et al., 2009; Mattei et al., 2014). But the pathogenesis of psoriasis remains unclear. Most studies suggested that psoriasis was a chronic inflammatory skin disease involving a variety of cells (Ota et al., 2014; Allen et al., 2001).

Liraglutide, glucagon-like peptide-1 receptor (GLP-1R) agonists, is a new drug for treating diabetes. GLP-1 is secreted by intestinal endocrine L cells that effectively stimulates the secretion of insulin, suppresses appetite and reduces intrahepatic lipid level. The GLP-1Rs are widely distributed on a variety of cells, such as islet cells, endothelial cells, neurocytes, adipocytes, etc., recent studies found that the keratinocytes expressed GLP-1R and liraglutide upregulated keratinocytes migration via PI3K/Akt activation (List et al., 2006). Some researches suggested that psoriasis was associated with an increased prevalence and incidence of diabetes (Armstrong et al., 2013a).Among diabetic patients, the use of regular insulin was an elevated risk of new-onset psoriasis (Wu et al., 2015). In one study, the Psoriasis Area and Severity Index (PASI) was improved in patients with type 2 diabetes and psoriasis following 6 weeks of GLP-1 analogue therapy (Hogan et al., 2011a; Buysschaert et al., 2014). Another study demonstrated that the dermal γδ T-cell number and IL-17 expression were decreased in patients treated with liraglutide (Buysschaert et al., 2014). However, the mechanism of liraglutide improved psoriasis remains unclear. Liraglutide was reported to be involved in suppressing inflammation in endothelial cells and improving endothelial dysfunction via adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) (Li et al., 2016). Another research showed that liraglutide reduced chronic inflammation as shown by reducing numbers of activated microglia and astrocytes, and reduced levels of tumor necrosis factor-α (TNF-α) and interleukin-

☆ Committed to the diagnosis and treatment of skin diseases, especially the immunotherapy of dermatitis.

* Corresponding author at: ChongQing Three Gorges Central Hospital, Department of Dermatology and Venerology, ROAD Xincheng, Number 165, ChongQing 404100, China.

E-mail address: zm09000@126.com (Z. Wang).

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1ß (IL-1β) in the hippocampus (Wang et al., 2018). In this study, lipopolysaccharide (LPS) was used to induce inflammatory response in keratinocytes, and we attempted to investigate the effects of liraglutide on keratinocytes apoptosis and inflammation.

2. Materials and methods

2.1. Materials

The MEM medium was purchased from Thermo Fisher Scientific Inc. (Waltham, USA), Fetal bovine serum (FBS) was purchased from Biological Industries (Jerusalem, Israel), Cell Counting Kit-8 (CCK-8) was provided from Beyotime Biotechnology (shanghai, China), The antibodies of anti-phospho-AMPKα (T172), anti-phospho-IKKα/βS176/S180, anti-phospho-NF-κBp65, anti-phospho-JAK2, anti-phospho-STAT3, anti-SOCS3, anti-GLP-1R and β-actin were obtained from Abcam (Cambridge, UK), TNF-α and IL-6 ELISA Kit were provided from R&D Systems (Minnesota, USA), BCA Protein Assay was purchased from Thermo Fisher Scientific Inc. (Waltham, USA), AICAR and Compound C (CC) were provided from Sigma-Aldrich (Burlington, USA), Liraglutide was provided from Novo Nordisk (Copenhagen, Denmark). The polyvinylidene fluoride membrane was provided from Millipore (Bedford, USA). The Western Lightning™ Chemiluminescence Reagent Plus was provided from Daktronics Biotech Co., Ltd. (Beijing, China).

2.2. Methods

2.2.1. Cell culture and treatments

The HaCat cells were cultured in MEM medium supplemented with 10% FBS streptomycin at 37 °C in a humidified atmosphere with 5% CO_2. LPS and liraglutide were directly dissolved in MEM. CC and AICAR were dissolved in dimethyl sulfoxide (DMSO) and diluted to the desired concentration with free-serum MEM (CC:10 μM; AICAR:2 mM). The BAS group was treated with MEM alone. The concentration of CC and AICAR were 10 nM and 2 mM for 30 min, respectively. The LPS group was treated with 150 ng/ml LPS for 16 h. The liraglutide group was treated with 100 nM liraglutide for 30 min. In the LPS + LIRAG group, the cells were stimulated by liraglutide for 30 min after pre-incubation with LPS for 16 h.

2.2.2. Cell viability assay

The cell proliferation of different concentration group was measured by the CCK-8 assay according to the manufacturer's protocol. The HaCat cells were collected and plated into 96-well plates at an density of 3×10^4 cells/well. The BAS, 10 nM, 50 nM, 100 nM, 200 nM group were established at the same time. After 30 min of incubation with the indicated drugs, 20 μl of CCK-8 reagent was added to 200 μl solution and incubated for 1–4 h. The supernatant was collected for measurement in a 450-nm enzyme immunoassay analyzer.

2.2.3. Western blotting

The HaCaT cells were seeded in 6-well plates , and at full confluence, cells were then treated with LPS or liraglutide. The protein lysate from cells were isolated with lysis buffer (1 mM Na_3VO_4, 1 μM protease inhibitor cocktail, 200 μM PMSF, 1 mM DTT, 100 mM NaF). Protein concentrations were determined by BCA protein assay reagent. Then the protein specimens were analyzed by SDS-PAGE on 7.5% polyacrylamide gel. The next step, the protein specimens were transferred to polyvinylidene fluoride membrane and probed with blocking solution for 2 h. Finally, the protein specimens were incubated with a variety of special antibodies and secondary antibodies followed by visualization with Western Lightning™ Chemiluminescence Reagent Plus. The protein expression was quantified by using National Institutes of Health (NIH) Image J software.

2.2.4. Trans-well assay

The HaCaT cells were cultured in the down-chamber of trans-well chamber and incubated with LPS or liraglutide. The macrophage RAW.264.7 were seeded in the up-chamber of trans-well chamber at an density of 5×10^4 cells/well. After 4 h of incubation, the trans-well chamber was washed with serum-free media, the macrophage were fixed and stained with H&E.

2.2.5. ELISA

After the HaCaT cells were treated with LPS or liraglutide, the culture supernatant was centrifuged at 3000 r.p.m. for 10 min at 4 °C. The TNF-α and IL-6 levels were measured with a ELISA Kit according to the manufacturer's protocol. Absorbency was detected at 450 nm.

2.2.6. Statistical analysis

All data were expressed as mean ± S.E. and calculated from three in dependent repeats. Two groups were compared using the Student's *t*-test and more than two groups were compared using ANOVA with Tukey's post-hoc test. Statistical analysis was performed using Prism 3.0 software. $P < .05$ is considered statistically significant.

3. Results

3.1. Keratinocytes expressed GLP-1R and liraglutide decreased cell viability in the HaCat cell

At first, the protein expression of GLP-1R was examined in the HaCaT cell by Western blot analysis. As shown in Fig. 1a, the keratinocytes expressed GLP-1R.

The effects of liraglutide on the viability of HaCaT cell were analyzed using the CCK-8 assay. Compared to the control group, the proliferation of HaCaT cells was significantly inhibited by liraglutide at concentrations of 100 nM and 200 nM after 16 h of treatment (74.82 ± 7.46, $P < .05$ vs. BAS; 49.30 ± 6.71, $P < .001$ vs. BAS, respectively) (Fig. 1b).

3.2. Effects of liraglutide on the inflammatory response of LPS in the HaCat cells

Next , inflammatory response in the HaCat cells was induced by LPS as psoriasis model in vitro. Liraglutide, as a new anti-diabetic agent, has been reported to have anti-inflammatory effects. The results demonstrated that the protein expression levels of p-IKKα/β S176/S180, p-NF-κB p65, p-JAK2, p-STAT3 and SOCS3 was increased significantly in LPS group compared with the BAS group (2.19 ± 0.10 ; 1.96 ± 0.07; 2.12 ± 0.12; 2.31 ± 0.07; 2.52 ± 0.04, $P < .001$ vs. BAS, respectively) (Fig. 2a–e). But in the LPS + LIRA group, the protein expression levels of p-IKKα/β S176/S180, p-NF-κB p65, p-JAK2, p-STAT3 and SOCS3 were lower compared with the LPS group (1.38 ± 0.08 vs. 2.19 ± 0.10; 1.40 ± 0.04 vs. 1.96 ± 0.07; 1.35 ± 0.05 vs.

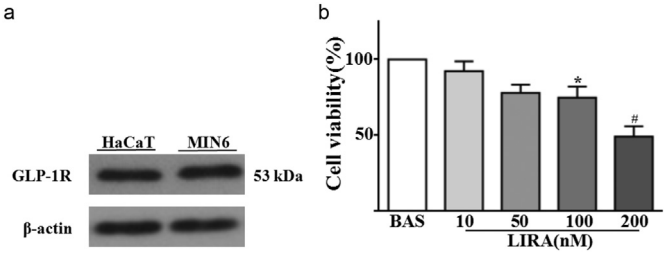

Fig. 1. Keratinocytes expressed GLP-1R and liraglutide decreased cell viability in the 2 HaCat cell. Western blot of GLP-1R (a). CCK-8 assay for detecting cell viability in 3 the HaCat cell treated with 10, 50, 100 and 200 nM liraglutide (LIRA) (b). Results are 4 the mean ± SE of six independent experiments. *$P < .05$, #$P < .001$ compared to 5 BAS group or as indicated.

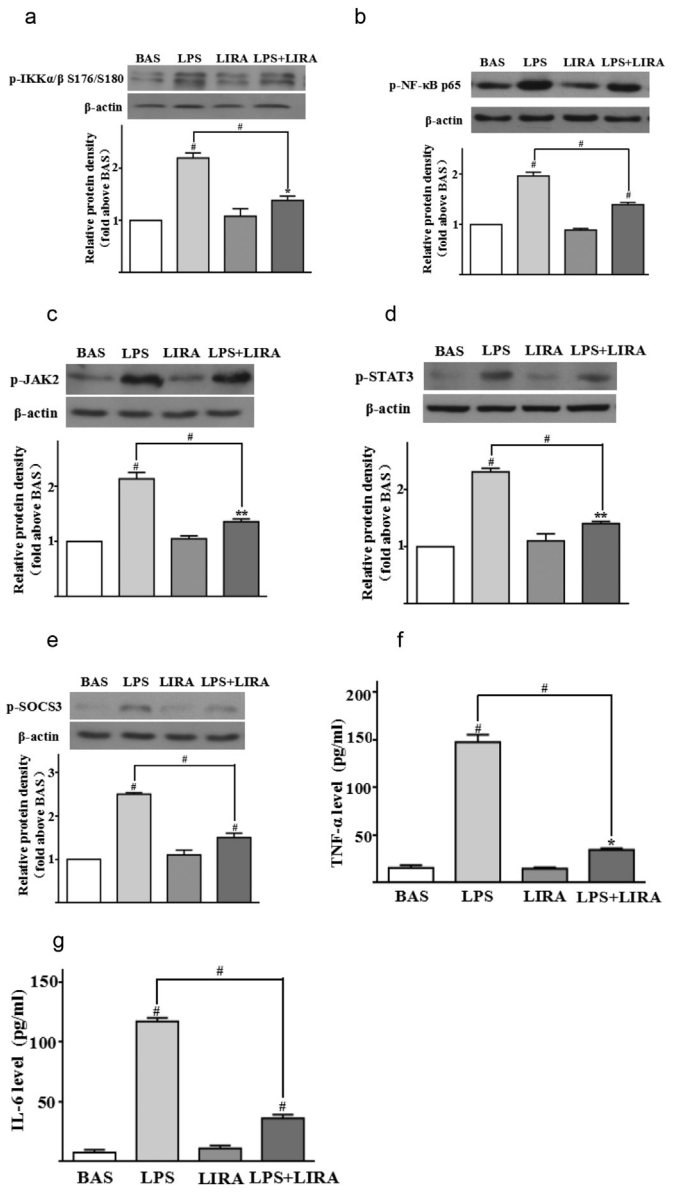

Fig. 2. Effects of liraglutide on the inflammatory response of LPS-induced in the 7 HaCat cell. The cells were treated with 100 nM liraglutide (LIRA) and 150 ng/ml LPS. 8 Western blot of phospho-IKKα/β S176/S180 (a), phospho-NF-κB p65 (b), 9 phospho-JAK2 (c), phospho-STAT3 (d) and SOCS3 (e). ELISA assay for detecting 10 the levels of TNF-α (f) and IL-6 (g) in the HaCat cell. Results are means ± SE of 11 six independent experiments. *$P < .05$, **$P < .01$, #$P < .001$ compared to BAS 12 group or as indicated.

2.12 ± 0.12; 1.41 ± 0.04 vs. 2.31 ± 0.07; 1.52 ± 0.10 vs. 2.52 ± 0.04, $P < .001$, respectively) (Fig. 2a–e). In addition, the LPS significantly increased TNF-α and IL-6 levels (147.51 ± 7.89 vs. 15.62 ± 2.76; 117.20 ± 3.17 vs. 7.66 ± 2.14, $P < .001$, respectively) (Fig. 2f-g). The levels of secreted TNF-α and IL-6 in the culture supernatant of the LPS + LIRA group were decreased significantly compared with the LPS group (34.42 ± 1.52 vs. 147.51 ± 7.89; 36.14 ± 3.08 vs. 117.20 ± 3.17, $P < .001$, respectively) (Fig. 2f–g). These results suggested that liraglutide inhibited the inflammatory response induced by LPS in HaCat cell.

3.3. Liraglutide restrained LPS-induced macrophage migration

Leukocyte adhesion and infiltration were the key trait in pathological mechanism of psoriasis. Then, the invasion ability was detected by

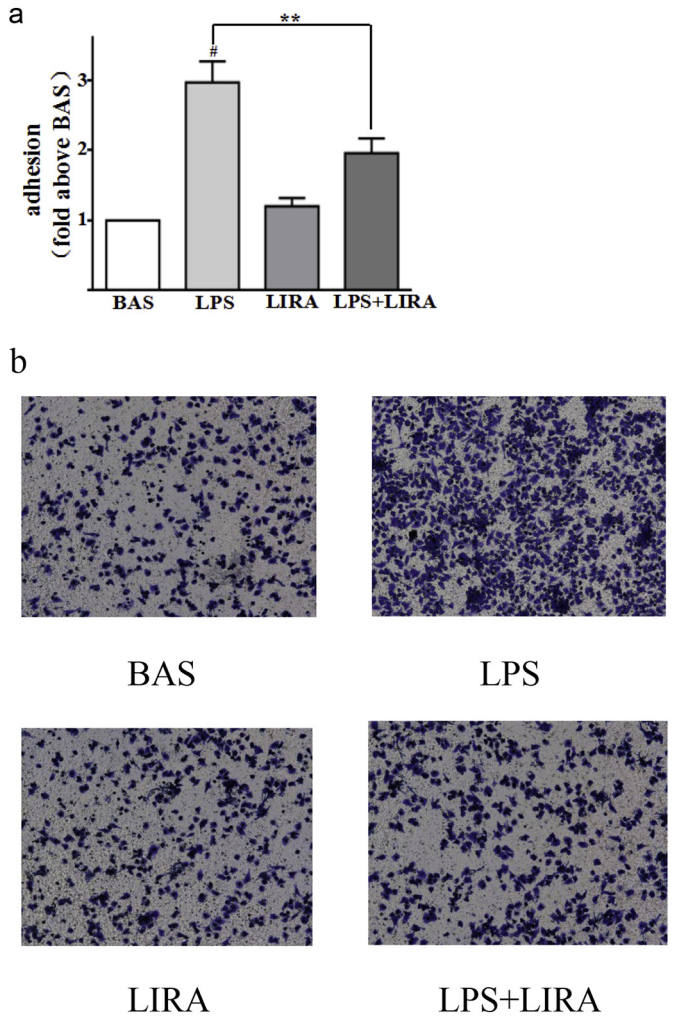

Fig. 3. Liraglutide restrained LPS-induced macrophages migration. Trans-well 14 assay for detecting the migration ability in the HaCat cell treated with 100 nM 15 liraglutide (LIRA) and 150 ng/ml LPS. Results are means ± SE of six independent 16 experiments. **$P < .01$, #$P < .001$ compared to BAS group or as indicated.

trans-well assay. The cell-straining indicated that the LPS increased the macrophage migration, the fold increase was 2.97 ± 0.30-fold ($P < .001$ vs. BAS). But the migration ability was attenuated remarkably by liraglutide (1.96 ± 0.21 vs. 2.97 ± 0.30, $P < .01$, LPS + LIRA group vs. LPS group). The results suggested that liraglutide inhibited the migration of macrophage to the HaCat cells (Fig. 3).

3.4. Inhibition of AMPK reversed the effects of liraglutide on the inflammatory response of LPS in the HaCat cell

Previous researches reported that liraglutide improved endothelial function and attenuated inflammation in endothelial cells through AMPK (Li et al., 2016). To examine the action of AMPK in LPS-induced inflammation in the HaCat cell, the inhibitor CC and the activator AICAR of AMPK were added. As shown in Fig. 4a, the phosphorylation of AMPK was the significantly inhibited by CC (47 ± 4%, $P < .001$ vs. BAS) and obviously activated by AIC (1.92 ± 0.07, $P < .001$ vs. BAS).

As shown in Fig. 4b, LPS decreased the AMPK phosphorylation by 44 ± 10% ($P < .01$ vs. BAS group). However, liraglutide reversed this effect and further increased the AMPK phosphorylation to 1.38 ± 0.06-fold ($P < .001$ vs. BAS group). We then detected whether liraglutide attenuated inflammatory response by activating AMPK. As expected, in the presence of LPS, CC impaired liraglutide-inhibited the

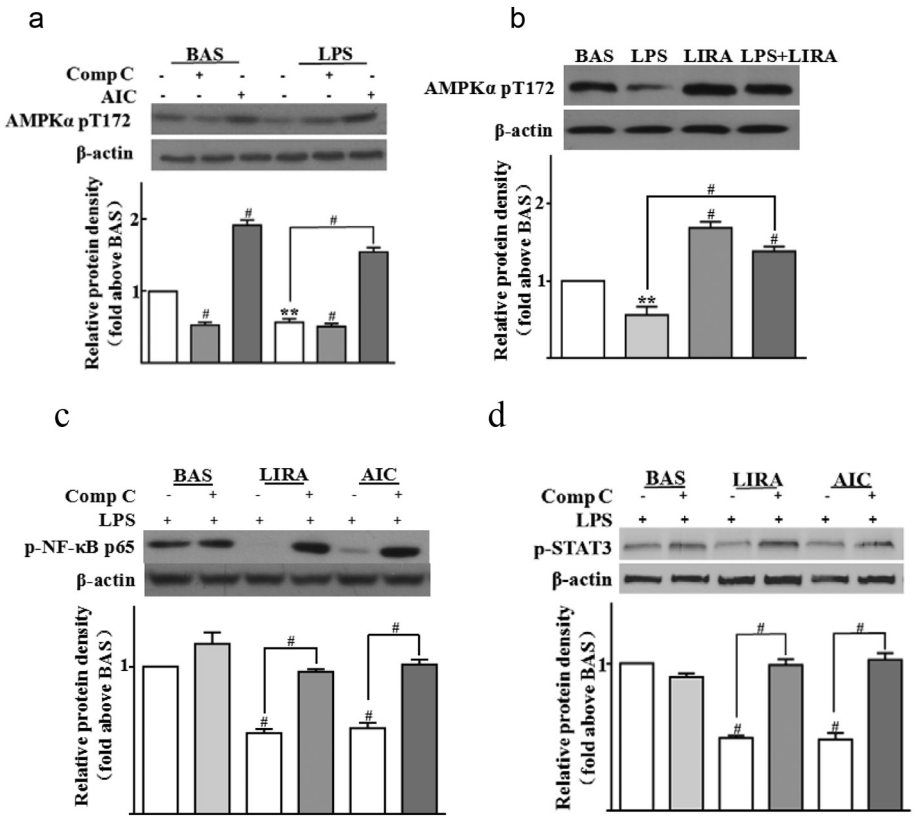

Fig. 4. Inhibition of AMPK reversed the effects of liraglutide on the inflammatory 18 response of LPS-induced in the HaCat cell. The cells were treated with Comp C for 19 30 min or AIC for 1 h for the measurement of phospho-AMPK (a, b), phospho-NF-κB 20 p65 (c) and phospho-STAT3 (d). Results are mean ± SE of five independent 21 experiments. $^{**}P < .01$, $\#P < .001$ compared to BAS group or as indicated.

phosphorylation of NF-κB p65. Compared to the LIRA + LPS group, the LIRA + LPS + CC group increased the level of p-NF-κB p65 (0.96 ± 0.02 vs. 0.55 ± 0.03, $P < .001$). And compared to the AIC + LPS group, the AIC + LPS + CC group increased the level of p-NF-κB p65 (1.01 ± 0.04 vs. 0.58 ± 0.03, $P < .001$) (Fig. 4c). The result was in accordance with p-STAT3 (Fig. 4d). These suggested that liraglutide decreased the LPS-sitimulated the protein levels of p-NF-κB p65 and p-STAT3 in an AMPK-dependent manner.

4. Discussion

Liraglutide, GLP-1 receptor agonist, was demonstrated that it was conducive to the treatment of psoriasis with type 2 diabetes according to the clinical controlled trial (Faurschou et al., 2014; Tobin et al., 2011b). Psoriasis often merges other diseases, such as obesity, metabolic syndrome, cardiovascular diseases, chronic obstructive pulmonary disease, autoimmune diseases and so on, diabetes is one of them. These diseases extremely affect the treatment and prognosis of psoriasis. A large number of studies were shown that diabetes and psoriasis maybe have a common molecular basis for the onset (Schadler et al., 2019; Armstrong et al., 2013b). Psoriasis is associated with insulin resistance, which is also considered as chronic low-grade inflammation. Both of them maybe have the same pathogenesis. As an antidiabetic drug, liraglutide is widely investigated for reducing blood glucose and increasing satiety, it can relieve chronic low-grade inflammation. Moreover, GLP-1R are widely expressed in many tissues, including skeletal muscles, endothelium and epidermis (Armstrong et al., 2013b). Some studies shown that GLP-1R agonist had anti-inflammatory effect and relieved the symptoms of psoriasis (Faurschou et al., 2014; Tobin et al., 2011b), but the underlying mechanism was not completely understood. In this study, we found that liraglutide could suppress proliferation in the HaCat cell, inhibit macrophage migration and diminish LPS-induced inflammation through AMPK.

Psoriasis is refractory skin disease characterized by hyper-proliferation and chronic inflammatory response. The abnormal differentiation of epidermal keratinocytes, parakeratosis, vascular formation and infiltration of inflammatory cells were essential to the pathophysiology of psoriasis (A et al., 2018). The inhibition of these cellular events is the key of psoriasis treatment. But the pathogenic mechanism of psoriasis has been unclear. The initial researches suggested that the primary cause of psoriasis was excessive hyperplasia of the skin and silvery white scales. But an increasing number studies found that there were a large number of monocytes and lymphocytes infiltration in the lesion of psoriasis, especially the infiltration of T lymphocytes in the dermis, it was central to the pathogenesis of psoriasis (Uyemura et al., 1993; Diani et al., 2014; Nickoloff, 2007). These evidences indicated that the pathogenesis of psoriasis was obviously related to the disorder of the immune system and chronic inflammation. The T lymphocytes are activated and differentiate into Th1, Th2 and Th17 cells, when they are stimulated with genetic, environmental and immunological factors. The initial T-cell imbalance promotes the release of inflammatory cytokines, such as IL-6, IL-22, IL-17 and TNF-α, then the inflammatory factors stimulate keratinocyte proliferation and angiogenesis (Pastore and Korkina, 2010; Emre et al., 2013). In addition, the inflammatory factors stimulate several pro-inflammatory signaling pathways, including nuclear factor kappa B (NF-κB), mitogen activated protein kinase (MAPK), and the Janus kinase–signal transducers and activators of transcription (JAK-STAT), then the signaling pathways increase the release of pro-inflammatory mediators , macrophage migration and expression of adhesion molecules. These cytokines can directly stimulate keratinocyte proliferation, expression of cell adhesion molecules and activate inflammatory signaling pathways, which lead to recurrent and worse psoriasis. Thus, the circulatory system of inflammatory response cascade is formed (Lynde et al., 2014), which aggravates the degree of psoriasis.

The NF-κB pathway has been well considered as a major pro-inflammatory signaling pathway for numerous pathological conditions (Lawrence, 2009; Rasheed and Haqqi, 2008). NF-κB complex is composed of RelA (p65), RelB, c-Rel, NF-κB1 (p105/p50) and NF-κB2 (p100/p52). When the IKKβ is phosphorylated, IκBs are degraded and

free NF-κB units, they are moved to the cell nucleus and regulate the transcription of DAN (Lawrence, 2009; Rasheed and Haqqi, 2008; Wang et al., 2017). In psoriasis, many studies strongly supported that the NF-κB signaling pathway was involved in the pathogenesis of psoriasis, and it regulated many major genes of apoptosis or pro-inflammatory cytokines in psoriasis (Goldminz et al., 2013; Derakhshan, 2011). Moreover, NF-κB may well act as a link between the T cell-mediated and keratinocyte-mediated concerning the pathogenesis of psoriasis (Tsuruta, 2009). Our study showed that liraglutide could inhibit LPS-induced the phosphorylation of IKKβ and NF-κB.

As a central regulator of inflammatory and immune responses, JAK-STAT pathway has recently emerged as a key player in the development and pathogenesis of psoriasis (Calautti et al., 2018). STAT3 is initially identified as Acute Phase Response Factor (APRF), and recognized as the main mediator of the functions of IL-6 in many different cell types. Its activation occurs not only downstream of all members of the IL-6 family, but also of a great number of other cytokines, growth factors and of many cytokines that are involved in the pathogenesis of psoriasis. Our study showed that liraglutide could inhibit LPS-induced the phosphorylation of JAK2, STAT3 and the expression of SOCS3.

In the skin and blood of psoriasis patients, a large number of inflammatory cytokines were detected, such as TNF-α and IL-6 (Brezinski et al., 2014). As TNF-α is well known to induce the expression of various other pro-inflammatory mediators and various other pro-inflammatory activities which further induces inflammatory network in the psoriatic lesions. Furthermore, anti-TNF-α therapy was found to be an effective treatment for plaque psoriasis and psoriatic arthritis patients (Kane and FitzGerald, 2004; Tobin and Kirby, 2005). Our study showed that liraglutide could decrease LPS-induced the secretion of TNF-α and IL-6. The invasion of inflammatory cells is the important traits of psoriasis. In this study, the invasion ability was detected using trans-well assay. The result showed that liraglutide could inhibit LPS-induced macrophage migration.

A large number of results indicated that GLP-1 could increase levels of cyclic adenosine monophosphate (cAMP), suppress inflammation in endothelial cells and improve endothelial dysfunction via AMPK (Hogan et al., 2011a; Li et al., 2016). In addition, one study showed that the level of cAMP in psoriatic epidermis of psoriasis patients was lower than that of normal people (Vali et al., 2005). In our study, we used the AMPK inhibitor CC and AMPK activator AICAR to detect the mechanism. The data showed liraglutide could activate AMPK with or without LPS. More importantly, CC could eliminated the function of liraglutide, it indicated that liraglutide relieved inflammatory response though activating AMPK.

In summary, we verified that liraglutide suppressed proliferation, inhibited macrophage migration, and impaired inflammation by the activation of AMPK. Our results put forward new views on the treatment of psoriasis.

Conflicts of interest

All authors declare no conflicts of interest.

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