Glucocorticoid-Induced Leucine Zipper Suppresses ICAM-1 and MCP-1 Expression by Dephosphorylation of NF-kB p65 in Retinal Endothelial Cells

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Vascular inflammation and endothelial cell injury are some of the main mechanisms involved in the development of retinal diseases such as ischemic retinal vasculopathy,1 diabetic retinopathy, and posterior uveitis.2 As an important part of the blood-tissue barrier, vascular endothelial cells play critical roles in the development of vascular inflammatory injury.2 In many pathological conditions, including bacterial infection,4 diabetic retinopathy,5 and retinal vein occlusion,6 retinal endothelial cell injury is the main cause of retinal vascular dysfunction, which may result in loss of vision. Stimulation of human vascular endothelial cells by lipopolysaccharide (LPS) could induce nuclear factor (NF)-κB activation and the release of inflammatory cytokines,7,8 especially monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-z. These inflammatory cytokines lead to a cascade of proinflammatory activities, which damage the blood-retinal barrier, ultimately resulting in retinal neuron damage and visual impairment.2 Accordingly, the administration of anti-inflammatory drugs, which suppress cytokine production, may provide a useful strategy to control vascular inflammation.

Glucocorticoid-induced leucine zipper (GILZ), first described in 1997 as a glucocorticoid-induced protein,9 has been reported to have anti-inflammatory activities. In particular, GILZ was reported to modulate several important proinflammatory signaling pathways and was used as a marker of the effects of glucocorticoids in T lymphocytes,10 B lymphocytes,11 monocyte-derived dendritic cells,12 and macrophages,13 for example. It was reported that GILZ was decreased in human degenerated aortocoronary14 and that GILZ overexpression suppressed inflammatory reactions in human umbilical vein endothelial cells (HUVECs).15 However, the anti-inflammatory effects of GILZ in retinal vascular endothelial cells has not been investigated. Therefore, we investigated the anti-inflammatory effects of GILZ in retinal vascular endothelial cells and determined its potential mechanism of action by using rat primary retinal microvascular endothelial cells (RMECs).
**METHODS**

**Cell Culture**

Rat primary RMECs were purchased from Cell Biologics Company (catalog no. No. RA-6065; Chicago, IL, USA). The cell line was recovered in accordance with the supplier’s instruction. Briefly, the cells were quickly thawed in a cryo-vial by incubating them in a 37°C water bath for less than 1 minute until there was only a small piece of ice left in the vial. The cells were then transferred to a sterile centrifuge tube and 8 to 10 mL of prewarmed cell culture medium (Complete Rat Endothelial Cell Medium, catalog no. M1266; Cell Biologics) was added to the tube. The cells were centrifuged at 200g for 5 minutes, the supernatant was discarded, and the cell pellet was resuspended in 6 mL cell culture growth medium. The resuspended cells were transferred to a T25 flask precoated with gelatin-based coating solution, and the T25 flask was placed in a humidified, 5% CO₂ incubator at 37°C. The culture medium was replaced the next day to remove nonadherent cells and replenish nutrients. The cell culture medium was then replaced daily once cells were more than 70% confluent.

**Stable Transfection of GILZ Recombinant Lentivirus in RMECs and Intact Retina**

Glucocorticoid-induced leucine zipper overexpression and silencing was achieved using GILZ overexpressing recombinant lentivirus (OE-GILZ-rLV) and short-hairpin RNA targeting GILZ recombinant lentivirus (shRNA-GILZ-rLV), respectively (Genomeditech Co., Ltd., Shanghai, China). Two blank recombinant lentiviruses (blank-rLV) were used: the control virus for shRNA-GILZ-rLV and the control virus for OE-GILZ-rLV. To induce stable RMEC transfection, the RMECs (at >80% confluence) were plated in a six-well plate and allowed to adhere overnight. The cells were then infected with OE-GILZ-rLV, shRNA-GILZ-rLV, or the relevant blank-rLV (1 × 10⁶ UT/mL; 3 μL) for 6 hours before replacing fresh RMEC culture medium. Cells were left for 72 hours before the subsequent experiments.

Male Sprague-Dawley rats (approximately 200 g, 6–8 weeks old) were maintained in a 12-hour light/12-hour dark cycle with free access to food and water. Rats were anesthetized by ketamine (80 mg/kg) and xylazine (10 mg/kg). To achieve stable transfection, 2 μL of the relevant lentivirus was intravitreally injected using a Hamilton micro-injector (Hamilton Co., Bonaduz, Grischun, Switzerland) under a dissecting microscope (66 Vision Tech Co., Suzhou, Jiangsu, China). Seventy-two hours after transfection, rats were given an intravitreal injection of LPS (125 ng/μL; 2 μL; Sigma-Aldrich Corp., St. Louis, MO, USA) or PBS (2 μL) as a control. Rats were killed by cervical dislocation under anesthesia induced by ketamine (80 mg/kg) and xylazine (10 mg/kg). Only one eye of each rat was chosen for experiment. All procedures in this study were approved by the Animal Ethics Committee of the Eye and ENT Hospital of Fudan University, China, and were conducted in accordance with ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All efforts were made to minimize the animals’ suffering and to reduce the number of animals used.

**Cell Stimulation**

Lipopolysaccharide was first dissolved in PBS (1 mg/mL) and then diluted in RMEC culture medium to concentrations of 10, 100, and 1000 mg/mL. Isoliensinine (98% by HPLC; Tianhaoyuan Biotech Co., Ltd., Tianjin, China) was also dissolved in dimethyl sulfoxide (DMSO) (32.78 mM) and then diluted in RMEC culture media to a concentration of 20 μM. The RMECs were then stimulated with LPS at the indicated concentrations and times, or with isoliensinine or isoliensinine plus LPS for 24 hours. Equal amounts of PBS or DMSO were added to the culture medium as controls for LPS or isoliensinine stimulation, respectively.

**Western Blotting**

At the end of the experiments, the retinas or RMECs were suspended in cell lysis buffer (Cell Signaling Technology, Beverly, MA, USA) containing phoshpatase and protease inhibitors (Roche Diagnostics, Indianapolis, IN, USA) and were stored at −80°C until further use. Nuclear proteins and cytoplasmic proteins were separated using NE-PER Nuclear and Cytoplasmic Extraction Reagents (Thermo Scientific, Rockford, IL, USA). Equal amounts of proteins were loaded and separated on SDS-PAGE and were transferred to polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). The membranes were blocked in 5% nonfat milk at room temperature for 1 hour and were then incubated with the following antibodies: rabbit anti-GILZ polyclonal antibody (1:500; Proteintech, Chicago, IL, USA), anti-MCP1 antibody (1:2512; Proteintech), anti-ICAM antibody 1A29 (ab171123; Proteintech), rabbit anti-p65 polyclonal antibody (1:500; Proteintech), phospho-NF-κB p65 (Ser536) rabbit monoclonal antibody (1:1000; Cell Signaling Technology), inhibitory κB (IκB) antigen (1:500; Proteintech), or rabbit anti-β-actin antibody (1:1000; Abcam, Cambridge, MA, USA) overnight. After washing the membranes three times, they were incubated with appropriate secondary antibodies followed by chemiluminescent detection (Pierce Biotechnology, Rockford, IL, USA). Chemiluminescent images were captured using a Kodak Image Station 4000 MM Pro (Carestream, Rochester, NY, USA) and analyzed with Image-Pro Plus (ver. 6.0; Media Cybernetics, Bethesda, MD, USA). The band intensity was quantified and normalized against internal controls. Densitometry ratios were normalized to either total β-actin or lamin B (nuclear protein) as appropriate.

**Enzyme-Linked Immunosorbent Assays of ICAM-1 and MCP-1**

The culture supernatant concentrations of ICAM-1 and MCP-1 were measured after LPS stimulation of RMECs using ELISA kits (Rat ICAM-1 [CD54] ELISA Kit; Rat MCP-1 [CCL2] ELISA Kit; RayBiotech, Norcross, GA, USA). The cell culture supernatant samples were measured without dilution. The absorbance of each well was measured on a microplate reader at 450 nm.

**Immunofluorescence**

The adherent RMECs were washed twice with PBS and fixed for 10 minutes with 4% formaldehyde at room temperature. Cells were blocked with blocking buffer containing 10% normal donkey serum, 10% normal goat serum, 0.3% Triton X, and 1% BSA for 1 hour at room temperature. Cells were incubated with rabbit anti-NF-κB p65 antibody (1:300; Abcam) overnight at 4°C followed by Alexa Fluor 555-conjugated goat anti-rabbit IgG (1:500; Invitrogen, Carlsbad, CA, USA) for 1 hour at room temperature. The antibodies were diluted in blocking buffer and cells were washed twice with PBS between incubations. Finally, cells were counterstained with 4,6-diamidino-2-phenylindole (DAPI) (Sigma-Aldrich Corp.) and examined under a laser confocal microscope (Leica Microsystems, Wetzlar, Hesse-Darmstadt, Germany).
Statistical Analysis

Statistical analyses were performed using SPSS for Windows Version 17.0 (SPSS, Inc., Chicago, IL, USA). The specific method has been described in each figure legend.

RESULTS

Lipopolysaccharide Downregulated GILZ Expression in RMECs

To determine whether LPS downregulated GILZ expression in retinal vascular endothelial cells, we measured the expression of GILZ in RMECs exposed to different concentrations of LPS (0, 10, 100, and 100 ng/mL) for 24 hours, or to 1000 ng/mL LPS for 0, 2, or 6 hours. As shown in Figure 1, LPS downregulated GILZ expression in RMECs in a dose- and time-dependent manner. Stimulation with LPS at 100 or 1000 ng/mL for 24 hours significantly decreased GILZ expression compared with control cells (Figs. 1A, 1B). In addition, stimulation with LPS at a concentration of 1000 ng/mL for 2 hours markedly decreased GILZ expression, and this decrease persisted for 6 hours (Figs. 1C, 1D).

Glucocorticoid-Induced Leucine Zipper Overexpression Inhibits NF-κB p65 Nuclear Translocation

Corticosteroid is the most important drug for treating ocular inflammatory diseases,16 and its anti-inflammatory effects are thought to be mediated by inhibition of the transcriptional activity of NF-κB.17,18 Because GILZ is an inducible target of glucocorticoids,9 several studies have demonstrated its involvement in the anti-inflammatory effects of glucocorticoids.10,19 Therefore, we investigated the effects of GILZ expression on NF-κB activation in retinal vascular endothelial cells. Glucocorticoid-induced leucine zipper overexpression was successfully induced in RMECs at 72 hours after OE-GILZ-rLV transfection (Figs. 2A, 2B). In RMECs transfected with blank-rLV, most p65 was located in the cytosol, with little nuclear p65 (Figs. 2C–F). Lipopolysaccharide stimulation (1000 ng/mL for 1 hour) significantly enhanced p65 translocation from the cytosol to the nucleus in blank-rLV–transfected RMECs and this effect of LPS was suppressed by GILZ overexpression (Figs. 2C–F). These findings obtained by Western blotting were also supported by immunofluorescence studies because p65 was hardly detected in the nuclei of unstimulated blank-rLV–transfected cells, whereas LPS induced a marked increase in nuclear p65 (Fig. 2G). Taken together, these results indicate that exogenous GILZ suppresses LPS-induced p65 translocation in RMECs.

Exogenous GILZ Inhibit NF-κB Translocation by Enhancing p65 Dephosphorylation

Because IκB degradation is a major signaling step leading to p65 translocation,18 we determined the expression of IκBα in

![Figure 1. Lipopolysaccharide downregulates GILZ expression in RMECs in a dose- and time-dependent manner. (A, B) Dose-dependent effect of LPS on GILZ expression. Retinal microvascular endothelial cells were treated with 0, 10, 100, or 1000 ng/mL LPS for 24 hours and GILZ protein expression was determined by Western blotting. (C, D) Time-dependent effects of LPS on GILZ expression. Retinal microvascular endothelial cells were treated with 1000 ng/mL LPS for 0, 2, or 6 hours and GILZ protein expression was determined by Western blot analysis; β-actin was used as the loading control. Quantitative analysis of GILZ, as determined by densitometric analysis, expressed as a ratio of β-actin. Data represent means ± SE; ANOVA with a Bonferroni post hoc test was used. *P < 0.05, **P < 0.01.](iovsvls.0633_f1a.png)
FIGURE 2. Glucocorticoid-induced leucine zipper overexpression inhibits LPS-induced NF-κB p65 nuclear translocation in RMECs. (A, B) Western blotting analysis of GILZ in RMECs transfected with overexpressing recombinant lentivirus (OE-GILZ-rLV) or blank-rLV for 72 hours. (C, D) Western blotting analysis of cytosolic p65 expression in blank-rLV or OE-GILZ-rLV transfected RMECs stimulated with LPS (1 hour at 1000 ng/mL). (E, F) Western blotting analysis of nuclear p65 expression in blank-rLV or OE-GILZ-rLV transfected RMECs stimulated with LPS (1 hour at 1000 ng/mL). (G) The localization of NF-κB p65 in blank-rLV or OE-GILZ-rLV transfected RMECs stimulated with LPS (1 hour at 1000 ng/mL) was assessed by immunofluorescence. Red indicates p65-stained and blue indicates DAPI-stained nuclei. Scale bar: 10 μm. β-actin was used as the loading control of cytosolic p65; Lamin B was used as the loading control of nuclear p65. Quantitative analysis, as determined by densitometric analysis, expressed as a ratio of loading control. Data represent means ± SE. ANOVA with a Bonferroni post hoc test was used for multiple groups. Mann-Whitney U test was used when two groups were compared. *P < 0.05, **P < 0.01.
blank-rLV– and OE-GILZ-rLV–transfected RMECs following LPS stimulation. As shown in Figures 3A and 3B, IκBα expression was decreased in RMECs stimulated with LPS for 1 hour. The expression of IκBα was not significantly different between blank-rLV–transfected RMECs and OE-GILZ-rLV–transfected RMECs, which indicates that the inhibitory effects of GILZ on NF-κB translocation are independent of IκBα degradation.

We next determined the p65 phosphorylation status, focusing on Ser536, which is known to alter the kinetics of p65 nuclear translocation.20 As indicated in Figures 3C and 3D, the level of phosphorylated (p)-p65 at Ser536 was significantly increased at 1 hour after LPS stimulation in blank-rLV–transfected RMECs. This LPS-induced increase in phosphorylated p65 was suppressed in OE-GILZ-rLV–transfected RMECs. This indicates that GILZ overexpression inhibited NF-κB p65 translocation by enhancing p65 dephosphorylation.

Glucocorticoid-Induced Leucine Zipper Overexpression Decreased LPS-Induced ICAM-1 and MCP-1 Expression in RMECs

As shown in Figure 1, LPS enhanced GILZ downregulation in RMECs, and this was accompanied by enhanced ICAM-1 and MCP-1 expression. As shown in Figures 4A–H, the expression levels of both cytokines increased in time- and LPS dose-dependent manners. Stimulation with LPS for 24 hours at 1000 ng/mL significantly increased ICAM-1 and MCP-1 expression compared with control RMECs (ICAM-1: 362.50 ± 44.91 vs. 204.84 ± 54.43 pg/mL; MCP-1: 32831 ± 3934.60 vs. 28107 ± 4050.05 pg/mL, respectively; both P < 0.001; Figs. 4I, 4J). As described above, LPS significantly decreased GILZ expression, but this decrease was suppressed by GILZ overexpression in RMECs (Figs. 5A, 5B). Glucocorticoid-induced leucine zipper overexpression also suppressed the increases in ICAM-1 and MCP-1 induced by LPS (24 hours at 1000 ng/mL) (Figs. 5C–F).

We next examined the impact of GILZ silencing for 72 hours. As shown in Figure 6A, GILZ expression was further reduced by LPS in shRNA-GILZ-rLV–transfected RMECs (Figs. 6A, 6B), and this was accompanied by significant increases in ICAM-1 and MCP-1 expression (Figs. 6C–F).

To confirm the changes in protein expression, we also performed ELISAs to measure the concentrations of ICAM-1 and MCP-1 in the culture media of blank-rLV–, OE-GILZ-rLV–, and shRNA-GILZ-rLV–transfected RMECs after stimulation with LPS or PBS. As shown in Figure 7 and Supplementary Table S1, the culture medium concentrations of ICAM-1 and MCP-1 were significantly reduced by GILZ overexpression and were increased by GILZ silencing in RMECs stimulated with LPS for 24 hours at 1000 ng/mL.

Taken together, these results indicate that GILZ regulates ICAM-1 and MCP-1 expression in RMECs.
Nuclear Factor–κB p65 Dephosphorylation Downregulates ICAM-1 and MCP-1 Expression in RMECs

We finally performed additional experiments to explore whether the phosphorylation status of p65 mediated the changes in ICAM-1 and MCP-1 expression in RMECs. It was previously reported that isoliensinine, an alkaloid derived from the embryos of *Nelumbo nucifera,* significantly enhanced dephosphorylation of NF-κB p65 at Ser536 in hepatocellular carcinoma cells. Consistent with that study, we showed that isoliensinine reduced p65 phosphorylation in LPS-stimulated RMECs (Figs. 8A, 8B). We then exposed blank-rLV– or shRNA-GILZ-rLV–transfected RMECs to PBS, LPS, or LPS plus isoliensinine. We found that isoliensinine successfully enhanced p65 dephosphorylation in blank-rLV– and sh-GILZ-rLV–transfected RMECs stimulated with LPS for 24 hours (Figs. 8C–8H). The dephosphorylation of p65 was accompanied by decreases in ICAM-1 and MCP-1 expression (Figs. 8E–8H). These results indicate that p65 dephosphorylation downregulates ICAM-1 and MCP-1 expression.

Exogenous GILZ Decreased Retinal ICAM-1 and MCP-1 Expression in LPS-Induced Uveitis

We next investigated the regulatory effects of GILZ on ICAM-1 and MCP-1 expression in vivo. Intravitreal injection of LPS significantly decreased retinal GILZ expression in blank-rLV–transfected retinas and this decrease was attenuated by OE-GILZ-rLV transfection (Figs. 9A, 9B). Consistent with results obtained using RMECs, the changes in GILZ expression were accompanied by changes in ICAM-1 and MCP-1 expression because LPS increased retinal ICAM-1 and MCP-1 expression in blank-rLV–transfected eyes and GILZ overexpression attenuated these increases (Figs. 9C–9F).
**DISCUSSION**

The roles of GILZ in mediating the anti-inflammatory effects of glucocorticoids have been investigated in various cell types and animal models of inflammatory diseases by researchers who used overexpression or depletion strategies.\(^\text{10,11,13,14}\) Owing to its strong upregulation by glucocorticoids in the thymus,\(^\text{9}\) early studies on GILZ focused on its effects on T lymphocytes,\(^\text{10}\) B lymphocytes, and macrophages,\(^\text{13}\) and revealed that GILZ inhibited NF-κB activity by suppressing its nuclear translocation. Some researchers also reported that GILZ exerted anti-inflammatory effects on endothelial cells,\(^\text{14,15}\) but the underlying mechanism differed from that in thymic cells. For example, Cheng et al.\(^\text{15}\) reported that, in HUVECs, exogenous GILZ did not affect p65 nuclear translocation and instead it inhibited NF-κB p65-DNA binding.

**FIGURE 5.** Glucocorticoid-induced leucine zipper overexpression inhibits LPS-induced ICAM-1 and MCP-1 expression in RMECs. Western blotting analysis was performed to determine the protein expression levels of GILZ (A, B), ICAM-1 (C, D), and MCP-1 (E, F) in RMECs transfected with blank recombinant lentivirus (blank-rLV) or OE-GILZ-rLV and stimulated with LPS (24 hours at 1000 ng/mL). β-actin was used as the loading control. Quantitative analysis, as determined by densitometric analysis, expressed as a ratio of β-actin. Data represent means ± SE, ANOVA with a Bonferroni post hoc test was used. \(n = 3\) for each group. *\(P < 0.05\), **\(P < 0.01\).

**FIGURE 6.** Glucocorticoid-induced leucine zipper silencing enhances LPS-induced ICAM-1 and MCP-1 expression in RMECs. Western blotting analysis was performed to determine the protein expressions levels of GILZ (A, B), ICAM-1 (C, D), and MCP-1 (E, F) in RMECs transfected with blank-rLV or shRNA-GILZ-rLV and stimulated with LPS (24 hours at 1000 ng/mL). β-actin was used as the loading control. Quantitative analysis, as determined by densitometric analysis, expressed as a ratio of β-actin. Data represent means ± SE, ANOVA with a Bonferroni post hoc test was used. \(n = 3\) for each group. *\(P < 0.05\), **\(P < 0.01\).
GILZ Inhibits Retinal ICAM-1 and MCP-1 Expression

As described above, GILZ overexpression induced p65 dephosphorylation and downregulated ICAM-1 and MCP-1 expression in LPS-stimulated RMECs. However, what is the relationship between p65 dephosphorylation and ICAM-1 and MCP-1 downregulation in RMECs? It was previously reported that isoliensinine, an alkaloid derived from the embryos of *Nelumbo nucifera*, enhanced the dephosphorylation of p65 at Ser536 in hepatocellular carcinoma cells. Consistent with that study, we found that isoliensinine reduced p65 phosphorylation at Ser536 in LPS-stimulated RMECs. However, any retinal cells can be transfected after lentivirus intravitreal injection, including retinal vessels. It means that inhibition of ICAM-1 and MCP-1 could mediate by retinal vascular endothelial cells or other retinal cells. At same time, kinds of retinal cells can secrete MCP-1 and ICAM-1 after LPS stimulation. So in our present study, we could not demonstrate that the downregulation of MCP-1 and ICAM-1 in retina was because of specific overexpression of GILZ in retinal vascular endothelial cells. However, the amount of ICAM-1 and MCP-1 in the whole retina was down in OE-GILZ-rLV transfected eyes at 24 hours after LPS intravitreal injection, no matter what kinds of cell had overexpressed GILZ. The virus vectors that can specifically transflect retinal vascular endothelial cells should be designed further to verify whether downregulation of MCP-1 and ICAM-1 is mediated by retinal endothelial cells in retina after LPS intravitreal injection.

As shown in Figure 7, GILZ overexpression downregulated ICAM-1 and MCP-1 expression in RMECs. The concentrations of ICAM-1 (A) and MCP-1 (B) in the culture supernatants were measured by ELISAs of RMECs transfected with blank-rLV, shRNA-GILZ-rLV, or OE-GILZ-rLV and stimulated with LPS (24 hours at 1000 ng/mL). An equal amount of PBS was added to the culture medium as a control. β-actin was used as the loading control. Quantitative analysis, as determined by densitometric analysis, expressed as a ratio of β-actin. Data represent means ± SE, ANOVA with a Bonferroni post hoc test was used. n = 20 for each group. *P < 0.05, **P < 0.01.
FIGURE 8. Isolienisin-induced dephosphorylation of NF-κB p65 attenuates LPS-induced expression of ICAM-1 and MCP-1 in RMECs. (A, B) Western blotting analysis of phosphorylated-p65 (Ser536) in RMECs treated with PBS, LPS, or LPS plus isolienisin (ISO). (C, D) Western blotting of phosphorylated-p65 (Ser536) in RMECs transfected with blank-rLV or OE-GILZ-rLV and treated for 24 hours with LPS or LPS plus isolienisin. Western blotting of ICAM-1 (E, F) and MCP-1 (G, H) expression in RMECs transfected with blank-rLV or sh-GILZ-rLV and treated for 24 hours with LPS or LPS plus isolienisin. β-actin was used as the loading control. Quantitative analysis, as determined by densitometric analysis, expressed as a ratio of β-actin. Data represent means ± SE, ANOVA with a Bonferroni post hoc test was used. n = 3 for each group. *P < 0.05, **P < 0.01.
CONCLUSIONS

Glucocorticoid-induced leucine zipper expression was significantly decreased by LPS in RMECs, and this decrease was accompanied by increased ICAM-1 and MCP-1 expression. Glucocorticoid-induced leucine zipper overexpression, as induced by OE-GILZ-rLV transfection, attenuated the nuclear translocation of NF-κB p65. This inhibitor effect of GILZ was independent of IκB and instead involved enhanced p65 dephosphorylation. Glucocorticoid-induced leucine zipper overexpression regulated ICAM-1 and MCP-1 expression in vitro and in vivo, via a mechanism involving enhanced p65 dephosphorylation.

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