MiR-222 inhibition alleviates Staphylococcal Enterotoxin B-induced inflammatory acute lung injury by targeting Foxo3

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Acute lung injury (ALI) is a common acute and severe disease in clinical practice. Staphylococcal Enterotoxin B (SEB) is a superantigen that can cause inflammatory ALI. MiR-222 has been demonstrated to be upregulated in SEB-induced inflammatory ALI, but its exact roles and functions remain ill-defined. In this study, SEB exposure led to inflammatory ALI and high expression of miR-222 in model mice and lung infiltrating mononuclear cells, but the inflammatory response and high expression of miR-222 were restored in miR-222−/− mice. Moreover, we investigated the roles of miR-222 in vitro and observed that the concentrations of inflammatory cytokines and the expression of miR-222 were all elevated in SEB-activated splenocytes and miR-222 inhibition reversed the effects. Foxo3 was confirmed as a direct target of miR-222. Interestingly, SEB exposure led to a decrease of Foxo3 expression, and Foxo3 knockdown partially reversed the promotion of Foxo3 and the inhibition of inflammatory cytokines induced by miR-222 inhibitor in SEB-activated splenocytes. Our data indicated that miR-222 inhibition could alleviate SEB-induced inflammatory ALI by directly targeting Foxo3, shedding light on the potential therapeutic of miR-222 for SEB-induced inflammation in the lung.

Keywords. ALI; SEB; miR-222; Foxo3; inflammation

1. Introduction

Staphylococcal Enterotoxin B (SEB) is a superantigen which is produced from certain staphylococcus aureus in food. SEB exposure seriously affects human health, such as by food poisoning, toxic shock and exaggerated immune response (Balaban and Rasooly 2000; Faulkner et al. 2005; Savransky et al. 2003). When SEB is inhaled, T lymphocytes are activated and proliferated in large quantities, and secrete a massive amount of inflammation cytokines, such as gamma interferon (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), interleukin 2 (IL-2) and tumor necrosis factor-α (TNF-α) (Bette et al. 1993; Kozono et al. 1995). Acute lung injury (ALI) is a respiratory disease and SEB can induce inflammatory ALI (Liu et al. 2009; Saeed et al. 2012). However, the current treatment strategies for SEB-induced inflammatory ALI are less effective and very limited. Thus, it is necessary to explore the molecular mechanisms underlying SEB-induced inflammatory ALI and discover novel targets for the treatment of SEB-induced inflammatory ALI.

MicroRNAs (miRNAs), a class of non-coding small RNAs with 18–25 nucleotides, play vital roles in the expression of target genes at the post-transcriptional level (Bartel 2004). Previous studies have shown that
some miRNAs are associated with the regulation of inflammatory response. For instance, Guo et al. proved that miR-497 could inhibit the secretion of inflammatory cytokines (including IL-6, IL-β and IFN-α) in lipopolysaccharide (LPS)-induced ALI (Guo et al. 2019). Rao et al. showed that miR-155 was induced by SEB and miR-155 inhibition could overturn SEB-induced inflammatory ALI (Rao et al. 2014). These findings demonstrated that miRNAs played different roles in inflammation. Rao et al. also claimed that miR-222 was abnormally upregulated in SEB-induced inflammatory ALI (Rao et al. 2014). But the roles and molecular mechanisms of miR-222 in SEB-induced inflammatory ALI have not been clarified.

Forkhead box O3 (Foxo3), a transcription factor, has been demonstrated to be related to the progression of many human diseases, such as ovarian cancer (Zhu et al. 2019), breast cancer (Ai et al. 2019) and pulmonary vascular remodel (Zhao et al. 2019). Moreover, Foxo3 was associated with inflammatory and immune responses (Dejean et al. 2009; Litvak et al. 2012). Lin et al. suggested that Foxo3 deficiency contributed to lymphoid hyperplasia, inflammatory transcriptional activity and activation of T cells (Lin et al. 2004). However, the function of Foxo3 in SEB-induced inflammatory ALI still needs to be investigated.

In this study, we first explored the functions of SEB in lung architecture and inflammatory cytokines secretion, and established inflammatory ALI models by exposing mice/splenocytes to SEB. Then the expression of miR-222 in lung infiltrating mononuclear cells of SEB-treated mice and SEB-activated splenocytes was detected. We also evaluated the functions and mechanisms of miR-222 and Foxo3 in inflammation by further function and mechanism analysis.

2. Materials and methods

2.1 Experimental mice

6–8 weeks old female C57BL/6 mice and miR-222−/− mice (miR-222 global knockout mice) were purchased from the Jackson Laboratory (Jackson Laboratory, Bar Harbor, Maine, USA). All mice were bred under a pathogen-free condition. The arterial blood pressure was monitored in wild-type and miR-222−/− mice and we observed that arterial blood pressure was higher in wild-type mice than in miR-222 knockout mice. The animal experiments were approved by the Animal Ethics Committee of Beijing Jishuitan Hospital and carried out according to the guidelines of the National Animal Care and Ethics Institution.

2.2 SEB administration

SEB (Toxin Technologies, Sarasota, FL, USA) was dissolved in sterile phosphate buffered saline (PBS; Sigma-Aldrich Crop, St. Louis, MO, USA) at a concentration of 2 mg/mL, as previously described (Saeed et al. 2012). Mice were randomly divided into groups of 5 mice. Every mouse in SEB, WT and miR-222−/− groups was exposed to 25 μL SEB (Toxin Technologies) by the intranasal (i.n) route and every control mouse was exposed to 25 μL PBS (Sigma-Aldrich Crop). After exposure for 48 h, the mice were euthanized.

2.3 Lung histopathology analysis

After mice were euthanized, lung tissues were obtained by surgical resection and fixed in 10% formalin (Tiangen, Beijing, China) overnight. Obtained lung tissues were embedded and cut into 5 μm serial sections. Then the sections were dissolved in xylene (Tiangen) and rehydrated in different concentrations of alcohol (including 100%, 95% and 90%) to deparaffinized. Subsequently, the sections were stained with hematoxylin and eosin (HandE; Tiangen) and evaluated using a Nikon E600 light microscope (Nikon Corporation, Tokyo, Japan).

2.4 Bronchoalveolar lavage fluid (BALF) collection

After 48 h of SEB (Toxin Technologies) exposure, mice were euthanized. The tracheae of the mice treated with SEB (Toxin Technologies) or sterile PBS (Sigma-Aldrich Crop) were tied with a suture and intact lungs were excised. Then the BALF was collected by injecting 1 mL sterile ice-cold PBS (Sigma-Aldrich Crop) into the lungs.

2.5 Isolation of lung-infiltrating cells

Mice were euthanized after 48 h of SEB exposure and lungs were collected and homogenized in 10 mL sterile PBS (Sigma-Aldrich Crop) using Seward Stomacher® 80 Biomaster (Seward, Davie, FL, USA). Then cell
suspending were washed with sterile PBS (Sigma-Aldrich Crop) and layered on Fiocoll Histopaque-1077 (Sigma-Aldrich Crop). Next, cells were isolated by density gradient centrifugation at room temperature with the brake off. The lung infiltrating mononuclear cells were collected and enumerated by the Trypan blue exclusion method (Sigma-Aldrich Crop) using a hemocytometer (VWR Scientific, Chester, PA, USA).

2.6 In vitro cell culture and transfection

Splenocytes used in this study were isolated from C57BL/6 mice and cultured in complete RPMI 1640 medium (Gibco, Carlsbad, CA, USA). Splenocytes were seeded into a 96-well plate at a density of 1.0×10^6 cells/well and stimulated with SEB (1 μg/mL; Toxin Technologies) or control sterile PBS (Sigma-Aldrich Crop) for 24 h. Then splenocytes were harvested.

MiR-222 mimic (miR-222) and its negative control (miR-NC), miR-222 inhibitor (anti-miR-222) and its negative control (anti-miR-NC), small interfering RNA (si-RNA) against Foxo3 (si-Foxo3) and scramble si-RNA (si-NC) were purchased from GenePharma (GenePharma, Shanghai, China). Then the transfection of SEB-stimulated splenocytes was carried out by HiPerfect Transfection Reagent (Qiagen, Inc., Valencia, CA, USA). At 24 h post-transfection, splenocytes were collected for the following experiments.

2.7 Enzyme-linked immunosorbent assay (ELISA)

The levels of inflammatory cytokines (including IL-2, MCP-1, IFN-γ and IL-10) in BALF or splenocytes supernatants treated as above were analyzed by Biolegend enzyme-linked immunosorbent assay (ELISA) Max kits (Biolegend, SanDiego, CA, USA) according to manufacturer’s protocols. The absorbance at 450 nm wavelength was measured using a microplate reader (Bio-Tek Instruments, Inc., Winooski, VT, USA).

2.8 Total RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from lung infiltrating mononuclear cells or splenocytes by Rneasy Mini kit (Qiagen, Inc.) according to the instructions of manufacturer and quantified by a NanoDrop2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Then the RNAs were reversely transcribed into cDNAs by a Transcriptional First Strand cDNA Synthesis kit (Roche, Indianapolis, IN, USA). QRT-PCR was performed using SYBR Green qPCR Master mix (Bio-Rad Laboratories, Hercules, CA, USA) and miR-222 expression was calculated using the 2^(-ΔΔCt) method. U6 was used as an internal control. The primers used in this study were listed as follows: miR-222 (forward) 5'-GGGGAGCTACATCTGGCT-3' and (reverse) 5'-TGCGTGTCGTGGAGTC-3'; U6 (forward) 5'-GCTTCGGCAGCACATATACTAAAAT-3' and (reverse) 5'-CGCTTCACGAATTTTGCGTGCAT-3'.

2.9 Dual-luciferase reporter assay

Dual-luciferase reporter assay was conducted to verify the interaction of miR-222 and Foxo3. In brief, the 3'-untranslated regions (3'-UTR) of Foxo3 containing the predicted binding sites of miR-222 or its mutant were amplified and introduced into pGL3-control vectors (Promega, Madison, WI, USA) to construct luciferase reporter vectors Foxo3-WT and Foxo3-MUT, respectively. Then Foxo3-WT or Foxo3-MUT was transfected into splenocytes together with miR-222 or miR-NC by DharmaFECT DUO transfection reagent (Thermo Scientific, Pittsburgh, PA, USA) following the manufacturer’s instructions. The luciferase activity was analyzed by a Dual-Luciferase Reporter Assay Kit (Promega) after splenocytes were transfected for 24 h.

2.10 RNA immunoprecipitation (RIP) assay

RIP assay was conducted by using EZMagna RIP kit (EMD Millipore, Billerica, MA, USA). Firstly, splenocyte lysates were incubated with magnetic beads conjugated with antibody against Argonaute2 (Ago2; Sigma-Aldrich Crop) or anti-immunoglobulin G (IgG; Sigma-Aldrich Crop), following incubated with Proteinase K (Sigma-Aldrich Crop). Finally, the expression level of Foxo3 was determined by qRT-PCR after RNAs were purified from IgG or Ago2 immunoprecipitation complex.

2.11 Western blot analysis

Total protein was extracted from splenocytes by using RIPA lysis buffer (Beyotime, Shanghai, China) and quantified by using the BCA Protein Assay Kit.
(Thermo Fisher Scientific). Each equal amount of protein samples was separated 10% SDS-PAGE gel and then transferred onto polyvinylidene difluoride (PVDF) membranes (EMD Millipore). Next, the membranes were blocked with 5% skim milk for 1 h and incubated at 4°C overnight with primary antibody anti-Foxo3 (Abcam, Cambridge, MA, USA) or β-actin (Abcam). Subsequently, the membranes were washed with Tris-buffered saline and Tween 20 (TBST) and incubated with horseradish peroxidase-conjugated secondary antibody at room temperature for 2 h. Protein was visualized by an enhanced chemiluminescence system (Pierce, Rockford, IL, USA) and quantified using ImageJ software.

2.12 Statistical analysis

All data obtained were analyzed using GraphPad Prism 7 software (GraphPad, San Diego, CA, USA). Individual experiments were carried out in triplicate and in vitro experiments were repeated at least three times. The data were depicted as means ± standard deviation (SD). The significance was analyzed by Student’s t-test or one-way analysis of variance (ANOVA). The difference was considered significant if \( P<0.05 \).

3. Results

3.1 SEB exposure led to inflammation and upregulation of matured miR-222 in the lung tissues of mice

In order to investigate the effect of SEB exposure on inflammatory response in vivo, the mice were euthanized, and lung sections were collected after 48 h of SEB exposure. Histopathological analysis of H&E-stained lung sections showed that there were more extensive infiltrating cells in SEB exposure group compared with control group (figure 1A). Then the levels of inflammatory cytokines (including IL-2, MCP-1, IFN-γ and IL-10) in the BALF were evaluated by ELISA assay. The data showed that the productions of IL-2, MCP-1, IFN-γ and IL-10 were all drastically increased in SEB exposure group compared with control group (figure 1B–E). Furthermore, qRT-PCR data indicated that matured miR-222 expression was obviously elevated after SEB exposure in the lungs (figure 1F). In addition, SEB-treated mice showed marked increase in mononuclear cells in the lungs compared to control groups (Figure 1G). And the relative expression level of matured miR-222 in lung infiltrating mononuclear cells was conspicuously elevated in reference to control groups (figure 1H). The results suggested that SEB exposure triggered inflammation in the lung sections and could be used to establish the inflammatory ALI model, and matured miR-222 was significantly elevated after SEB exposure.

3.2 MiR-222 knockout alleviated SEB-induced inflammation in the lung tissues of mice

Since miR-222 was apparently upregulated after mice were exposed to SEB, we speculated that miR-222 was involved in SEB-stimulated inflammatory ALI. To explore the role of miR-222 in SEB-induced inflammation, WT mice and miR-222−/− mice were exposed to SEB for 48 h. Then the expression of miR-222 in the lung infiltrating mononuclear cells from WT mice or miR-222−/− mice was determined by qRT-PCR and the data indicated that miR-222 expression was notably decreased in miR-222−/− mouse group when compared to WT mouse group (figure 2A). Histopathological analysis of H&E-stained lungs sections showed that the lung architecture was almost restored to a normal state with little infiltrating cells in miR-222−/− mouse group compared to WT mouse group (figure 2B). Furthermore, ELISA assay revealed that the concentrations of inflammatory cytokines (including IL-2, MCP-1, IFN-γ and IL-10) were all markedly reduced in the BALF of miR-222−/− mice compared to those in WT mice (figure 2C–F). Besides, we observed that the number of mononuclear cells in the lungs of miR-222−/− mouse group was reduced compared to WT group (figure 2G). Collectively, these results demonstrated that the knockout of miR-222 could alleviate SEB-induced inflammatory ALI.

3.3 SEB exposure induced inflammation and upregulation of miR-222 in vitro

To reveal whether SEB exposure could lead to inflammatory response and abnormal expression of miR-222 in vitro, splenocytes were exposed to 1 μg/mL SEB for 24 h in vitro. ELISA assay was conducted to measure the levels of inflammatory cytokines. As a result, the levels of IL-2, MCP-1, IFN-γ and IL-10 were all distinctly increased in SEB-treated splenocytes compared to control splenocytes (figure 3A–D). Then the expression of miR-222 was measured by qRT-PCR and we found that SEB exposure resulted in a
significant increase of miR-222 expression in splenocytes (figure 3E). Taken together, SEB exposure triggered inflammation and high expression of miR-222 in splenocytes in vitro.

3.4 Inhibition of miR-222 alleviated SEB-induced inflammation in vitro

To confirm the effect of miR-222 on SEB-induced inflammatory response in vitro, anti-miR-222 or anti-miR-NC was transfected into SEB-activated splenocytes. Then the expression of miR-222 was detected by qRT-PCR to evaluate transfection efficiency. We observed that anti-miR-222 led to a significant reduction of miR-222 level in SEB-activated splenocytes compared to anti-miR-NC transfected group (figure 4A). Moreover, we found the levels of IL-2, MCP-1, IFN-γ and IL-10 were all greatly diminished in SEB-activated splenocytes after anti-miR-222 transfection compared to those in anti-miR-NC transfected group (figure 4B–E). These data suggested that miR-222 downregulation could suppress SEB-stimulated inflammation in vitro.

3.5 MiR-222 directly targeted to Foxo3 and negatively regulated its expression in SEB-activated splenocytes

It has been reported that miRNAs regulate gene expression mainly by binding to the 3’-UTR of target mRNA (Bartel 2004). Thus, we explored the target gene of miR-222 by bioinformatics software DIANA-microT-CDS and found that Foxo3 was a potential target gene of miR-222 and miR-222 could bind to the 3’-UTR of Foxo3 (located on chromosome 10: 42148712–42184731 of Foxo3 3’UTR) (figure 5A). Then dual-luciferase reporter assay and RIP assay were conducted to confirm this prediction. The results of dual-luciferase reporter assay displayed that the luciferase activity was inhibited by Foxo3-WT and miR-222 co-transfection compared to Foxo3-WT and miR-NC co-transfection in SEB-activated splenocytes, but the luciferase activity was not changed in Foxo3-MUT group (figure 5B). The data of RIP assay showed that Foxo3 was enriched in Ago2 immunoprecipitation complex after miR-222 transfection compared to miR-NC transfection (figure 5C). Besides, we observed that SEB exposure led to a significant decrease of the
protein level of Foxo3 in splenocytes (figure 5D). Next, miR-222, miR-NC, anti-miR-222 or anti-miR-NC was transfected into SEB-activated splenocytes and the protein level of Foxo3 was analyzed by western blot analysis. As a result, miR-222 caused a significant decrease of Foxo3 and anti-miR-222 caused a significant increase of Foxo3 in SEB-activated splenocytes (figure 5E). Taken together, miR-222 could bind to Foxo3 and regulate Foxo3 expression.

3.6 Foxo3 knockdown partially reversed the effect of miR-222 inhibition on SEB-induced inflammation in splenocytes

As presented in figure 6A, si-Foxo3 transfection distinctly decreased the protein level of Foxo3 compared to that in si-NC transfected cells. Next, to determine whether miR-222 could regulate SEB-induced inflammation by targeting Foxo3 in splenocytes, we transfected anti-miR-
222, anti-miR-NC, anti-miR-222+si-Foxo3 or anti-miR-222+si-NC into SEB-activated splenocytes. Western blot analysis was conducted to detect the expression of Foxo3. We found that Foxo3 protein expression was markedly upregulated by anti-miR-222, while this increase was eliminated by si-Foxo3 (figure 6B). Of note, the concentrations of IL-2, MCP-1, IFN-γ and IL-10 in SEB-activated splenocytes were all diminished after anti-miR-
222 transfection, but these effects were partially restored by si-Foxo3 transfection (figure 6C–F). These results indicated that miR-222 inhibition alleviated SEB-induced inflammation by targeting Foxo3 in vitro.

3.7 MiR-222 overexpression promoted SEB-induced inflammation in splenocytes by downregulating Foxo3 expression

Based on all the experimental results, we established a potential regulatory network in regulating SEB-induced inflammation. MiR-222 could directly interact with Foxo3 and negatively regulate Foxo3 expression. Moreover, miR-222 overexpression enhanced the levels of IL-2, MCP-1, IFN-γ and IL-10 in SEB-activated splenocytes by targeting Foxo3, indicating that miR-222 played a positive role in SEB-induced inflammatory ALI (figure 7).

4. Discussion

ALI is the injury of alveolar epithelial cells and capillary endothelial cells, which can result in diffuse pulmonary interstitial, alveolar edema and acute
hypoxic respiratory dysfunction (Ware and Matthay 2000). Although many advances have been made, the mortality rate of ALI is still very high (Dushianthan et al. 2011). Therefore, it is important to discover new treatment methods for ALI. Previous studies have demonstrated that SEB can induce cellular infiltration, cytokine secretion, tissue damage and edema, and so SEB was used to establish inflammatory lung injury models (Rao et al. 2014; Wheeler and Bernard 2007).

In our current study, we exposed mice or splenocytes in SEB to establish inflammatory ALI models and then detected the levels of inflammatory cytokines (including IL-2, MCP-1, IFN-γ and IL-10) in the BALF and splenocytes by ELISA assay. We found that the concentrations of IL-2, MCP-1, IFN-γ and IL-10 were all increased in SEB-stimulated BALF and splenocytes. Moreover, lung architecture was destroyed with more infiltrating cells. These findings were in line with the studies of Alghetaa et al. (2018) and Rao et al. (2015a, b).

In addition, we observed that miR-222 expression was apparently elevated by SEB exposure, and its expression was significantly inhibited in the lung infiltrating mononuclear cells from SEB-treated miR-222−/− mice and in anti-miR-222 transfected SEB-activated splenocytes. Moreover, miR-222 inhibition lessened infiltration in the lung sections and alleviated SEB-stimulated inflammatory response in the BALF and splenocytes. A report verified that miR-17–92 cluster was overexpressed in SEB-mediated lungs and Δ⁹ Tetrahydrocannabinol (THC) could restore SEB-induced inflammatory ALI by suppressing miR-17–92 cluster expression (Rao et al. 2015a, b). Rao et al. indicated that miR-222 was highly expressed in the lungs after SEB exposure (Rao et al. 2014) and Elliott et al. also demonstrated that miR-222 was upregulated in SEB-induced ALI mice model and involved in the anti-inflammation effect of 3,3'-Diindolylmethane (DIM) (Elliott et al. 2016). These findings provided evidence that miR-222 was induced by SEB and played a vital role in SEB-induced inflammatory ALI, which supported our results in this study.

MiRNAs have been demonstrated to exert their functions by binding to the 3'-UTR of their target mRNA, leading to the inhibition of translation or the degradation of target mRNA (Bartel 2004). For example, miR-222 contributed to colorectal cancer cell migration and invasion through targeting MST3 (Luo et al. 2019). In this study, we confirmed that Foxo3 was a direct target of miR-222 and Foxo3 expression was drastically decreased by SEB exposure in splenocytes. Alternatively, we identified the roles and mechanisms of miR-222 and Foxo3 in SEB-induced inflammatory ALI. As we observed, Foxo3 expression was inhibited by miR-222 and promoted by anti-miR-222 in SEB-activated splenocytes. Furthermore, knockdown of Foxo3 partially restored the secretion of IL-2, MCP-1, IFN-γ and IL-10 mediated by miR-222 inhibition in SEB-activated splenocytes, indicating that miR-222 regulated SEB-induced inflammation by targeting Foxo3. A large number of studies have shown that Foxo3 is involved in inflammation (Hwang et al. 2011; Lin et al. 2004; Snoeks et al. 2009; Viatte et al. 2016). Kuo et al. manifested that Foxo3 could be targeted by miR-92a and its elevation promoted anti-inflammatory effect in human osteoarthritis synovial fibroblasts (Kuo et al. 2019). Wu et al. declared that miR-155 promoted inflammatory response in renal ischemia-reperfusion injury model by repressing Foxo3 expression (Wu et al. 2016). Kim et al. disclosed that deficiency of Foxo3 induced the production of pro-inflammatory via acting as a target of miR-132 and miR-223 in inflammatory bowel disease (Kim et al. 2016). Moreover, Roshni Rao et al. demonstrated that SEB led to a significant downregulation of Foxo3, but miR-132 inhibitor restored this effect in splenocytes; besides, miR-132 led to an increase of inflammatory cytokines.

![Figure 7. Potential mechanism of miR-222 implicated in inflammatory response in SEB-induced inflammatory ALI. Overexpression of miR-222 directly targeted Foxo3 to induce inflammatory response in SEB-induced ALI model.](image-url)
production by targeting Foxo3 (Roshni Rao et al. 2015a, b). All these reports indicated that Foxo3 was a negative regulator of inflammation in diseases and our results in the present study were consistent with these previous reports.

In conclusion, we highlighted the function of miR-222 in SEB-triggered inflammatory ALI and explored the association between miR-222 and Foxo3 in SEB-activated splenocytes. We demonstrated that miR-222 was upregulated in the lung sections and splenocytes after SEB exposure, and miR-222 inhibition suppressed inflammatory response by binding to Foxo3 in SEB-activated splenocytes. These findings supported the potential role of miR-222 as a therapeutic target for the treatment of SEB-induced inflammatory ALI.

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