HMBOX1 attenuates LPS-induced periodontal ligament stem cell injury by inhibiting CXCL10 expression through the NF-κB signaling pathway

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Abstract. Homeobox containing 1 (HMBOX1) is a member of the homeobox transcription factor family that has been reported to serve an important role in numerous biological processes. The present study aimed to determine the role of HMBOX1 in the pathogenesis of periodontitis. Human periodontal ligament stem cells (hPDLSCs) were treated with lipopolysaccharide (LPS) and transfected with a HMBOX1 overexpression (Ov-HMBOX1) plasmid or small interfering (si)-C-X-C motif chemokine ligand 10 (CXCL10) plasmids. The effects of Ov-HMBOX1 on cell proliferation, inflammation and apoptosis were subsequently investigated using Cell Counting Kit-8, ELISA for analysis of IL-6, TNF-α and IL-1β levels, TUNEL and western blotting assays for analysis of Bcl-2, Bax, cleaved caspase-3 and caspase-3 levels, respectively. Furthermore, the potential effects of HMBOX1 on the mRNA and protein levels of CXCL10 and the NF-κB signaling pathway were investigated by using reverse transcription-quantitative PCR and western blotting. Finally, the physiological processes of lipopolysaccharide (LPS)-induced hPDLSCs were assessed following treatment with phorbol 12-myristate 13-acetate (PMA), a NF-κB agonist. The results revealed that Ov-HMBOX1 transfection promoted proliferation whilst alleviating inflammation and apoptosis in LPS-induced hPDLSCs. Ov-HMBOX1 reduced the expression of CXCL10 by suppressing the NF-κB signaling pathway. PMA treatment inhibited the proliferation of LPS-induced hPDLSCs transfected with Ov-HMBOX1, which was reversed by transfection with si-CXCL10. In conclusion, results of the present study provided evidence that HMBOX1 can attenuate LPS-induced hPDLSC injury by downregulating CXCL10 expression via the NF-κB signaling pathway, which may provide a novel insight into the development of potentially novel treatment strategies for periodontitis.

Introduction

Periodontitis is one of the most common chronic inflammatory diseases and is characterized by the progressive destruction of the supporting tissues surrounding the tooth, eventually leading to tooth loss (1-3). Due to the lack of clear symptoms, the majority of patients typically miss the early intervention period of this disease, meaning that extensive damage has already been caused to the entire dentition on presentation (4). A review has previously revealed an association between periodontitis and diabetes complications in the human body (5). Periodontitis is traditionally treated using non-surgical methods, which mainly involve the subgingival eradication of bacterial deposits on the dental surface (6). However, deeper understanding on the etiopathogenesis of the disease is required to developnovelly effective treatment options (1).

Homeobox containing 1 (HMBOX1) is a member of the homeobox transcription factor family that has been identified to serve a role in a large number of biological processes including proliferation, inflammation and apoptosis (7-10). A previous genomic and proteomic analysis found that the expression levels of HMBOX1 were downregulated in gingival tissues from patients with periodontitis compared with a control group without periodontitis, which identified a potential association between HMBOX1 expression levels and the pathogenesis of periodontitis (11). In addition, mice deficient in HMBOX1 exhibited enhanced levels of apoptosis in vascular endothelial cells following challenge with lipopolysaccharide (LPS), which promoted the inflammatory response in a mouse model of acute lung injury (10,12). However, to the best of our knowledge, no studies to date have determined the specific role of HMBOX1 in the pathogenesis of periodontitis. CXCL10 was first identified in 1985 and has been found to be regulated by various cytokines, such as IFN-γ and...
TNF (13-16). It has been previously reported that the significantly upregulated expression of CXCL10 in patients with periodontitis can serve as a biomarker of periodontitis (17). In addition, the NF-κB signaling pathway was found to upregulate the expression of CXCL10 in COMM domain-containing protein 7-treated hepatocellular carcinoma cells (18). Aldo-keto reductase family 1 member C2 was also discovered to exert potent anti-inflammatory and antioxidant effects by inhibiting NF-κB activity downstream of HMBOX1 activation in an atherosclerosis model of LPS-induced EA.hy926 cells (9).

Therefore, it was hypothesized in the present study that HMBOX1 may alleviate LPS-induced human periodontal ligament stem cell (hPDLSC) injury by downregulating CXCL10 expression via the NF-κB signaling pathway.

Materials and methods

Cell lines and culture. Human periodontal stem cells (hPDLSCs) were purchased from YBIO (cat. no. YB-Cell-H002) and cultured in DMEM (Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% FBS (Gibco; Thermo Fisher Scientific, Inc.) cultured in DMEM (Gibco; Thermo Fisher Scientific, Inc.) were purchased from YBIO (cat. no. YB-Cell-H002) and Materials and methods

Reverse transcription-quantitative PCR (RT-qPCR). Total RNA was extracted from hPDLSCs using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.), CXCL10 (cat. no. EK0410) and IL-1β (cat. no. EK0392) were determined using their corresponding ELISA kits (Wuhan Boster Biological Technology Ltd.) according to the manufacturer's protocols.

TUNEL assay. Apoptosis was conducted using an In Situ Cell Death Detection Kit (Roche Diagnostics) according to the manufacturer's protocol. The cells were fixed with 4% paraformaldehyde for 30 min at room temperature, followed by the permeation of 0.2% Triton X-100 for 8 min at room temperature. TUNEL solution was dropped into sections for incubation for 60 min at 37°C, which were then washed
with PBS for three times, each for 5 min and the nuclei were stained using DAPI for 8 min (0.4 µg/mL) in the dark. Apoptotic cells in four randomly selected views were visualized using an inverted fluorescence microscope (IX73; Olympus Corporation; magnification, x200). The apoptotic index (%) was calculated using the following formula: Apoptotic cells (green fluorescence)/total cells (blue fluorescence) x100%.

**Statistical analysis.** Statistical analysis was performed using GraphPad Prism version 6.0 software (GraphPad Software, Inc.) and data are presented as the mean ± SD. Statistical differences between ≥3 groups were determined using one‑way ANOVA followed by Tukey's test. All experiments were repeated at least three times. P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Overexpression of HMBOX1 promotes the proliferation of LPS‑induced hPDLSCs.** To determine the role of HMBOX1 in the pathogenesis of periodontitis, the expression levels of HMBOX1 were first measured in LPS‑treated hPDLSCs. As shown in Fig. 1, exposure of hPDLSCs to LPS for 12 or 24 h significantly downregulated the mRNA and protein expression levels of HMBOX1 compared with those in hPDLSCs without LPS treatment.

Subsequently, transfection of hPDLSCs with Ov‑HMBOX1 significantly increased the expression of HMBOX1 compared with that in the control and Ov‑NC groups (Fig. 2A). Furthermore, results from the CCK‑8 and western blot analyses demonstrated that LPS exposure significantly reduced the viability of hPDLSCs and expression levels of the proliferation‑related proteins Ki‑67 and PCNA (Fig. 2B). By contrast, Ov‑HMBOX1 significantly reversed all aforementioned effects on cell viability and Ki‑67 and PCNA expression (Fig. 2B and C). These results suggest that HMBOX1 overexpression can restore the proliferation of LPS‑induced hPDLSCs.

**Overexpression of HMBOX1 inhibits inflammation and apoptosis in LPS‑induced hPDLSCs.** Since periodontitis is one of the most prevalent inflammatory diseases (21), the effects of HMBOX1 on the inflammation and apoptosis of LPS‑induced hPDLSCs were analyzed. LPS stimulation significantly increased the production and expression of inflammatory cytokines IL‑6, TNF‑α and IL‑1β, which was significantly reversed by Ov‑HMBOX1 transfection (Fig. 3A and B). LPS stimulation also significantly increased the apoptosis of hPDLSCs, whilst significantly downregulating the expression levels of the anti‑apoptotic proteins Bcl‑2. However, expression of the proapoptotic proteins Bax and cleaved caspase‑3 were significantly increased y LPS treatment (Fig. 3C and D). Conversely, these observations aforementioned were significantly reversed after these LPS‑induced hPDLSCs were transfected with Ov‑HMBOX1 (Fig. 3C and D). These findings suggest that HMBOX1 overexpression can inhibit the inflammation and apoptosis of LPS‑induced hPDLSCs.

**HMBOX1 modulates the expression of CXCL10 by regulating the NF‑κB signaling pathway.** To investigate the effects of HMBOX1 on CXCL10 expression and the NF‑κB signaling pathway in LPS‑induced hPDLSCs, western blotting and RT‑qPCR were used to measure CXCL10 expression levels following the overexpression of HMBOX1. The results revealed that Ov‑HMBOX1 transfection significantly downregulated the expression levels of CXCL10 compared with those in cells transfected with Ov‑NC (Fig. 4A). Furthermore, LPS‑induced phosphorylation of p65 and IkBα was significantly abrogated by Ov‑HMBOX1 transfection (Fig. 4B), suggesting a possible association between HMBOX1 and the NF‑κB signaling pathway. Therefore, a NF‑κB agonist, PMA, was used to assess the potential effects of NF‑κB on the regulation of CXCL10 expression. The significant suppressive effects of Ov‑HMBOX1 on the expression of CXCL10 were significantly reversed by PMA (Fig. 4C). These findings suggest that HMBOX1 may modulate the expression of CXCL10 by regulating the NF‑κB signaling pathway.

**HMBOX1 enhances the proliferation whilst inhibiting the inflammation and apoptosis of LPS‑induced hPDLSCs through the NF‑κB/CXCL10 axis.** Based on the aforementioned findings, it was hypothesized that HMBOX1...
may influence the physiology of LPS-induced hPDLSCs through the NF-κB/CXCL10 signaling axis. The expression of CXCL10 was knocked down using si-CXCL10-1 and si-CXCL10-2. si-CXCL10-2 was selected for use in subsequent experiments as it was able to significantly downregulate CXCL10 expression, with a markedly greater magnitude compared with that mediated by si-CXCL10-1 (Fig. 5A). PMA treatment inhibited the proliferation of hPDLSCs in LPS+Ov-HMBOX1+PMA+si-NC group compared with LPS+Ov-HMBOX1+si-NC group, which was significantly abolished by co-transfection with si-CXCL10 (Fig. 5B). Furthermore, the protein levels of proliferation markers, Ki67 and PCNA, were significantly decreased by PMA treatment compared with that in the co-treatment of LPS and Ov-HMBOX1 transfection, but were able to be markedly reversed by CXCL10 silencing (Fig. 5C).

The inflammation and apoptosis of hPDLSCs in LPS+Ov-HMBOX1+PMA+si-NC group were enhanced by PMA as relative to LPS+Ov-HMBOX1 group, as evidenced by the increased production and secretion of inflammatory cytokines IL-6, TNF-α and IL-1β (Fig. 6A and B) and the increased apoptotic rate of these cells. In addition, increased expression levels of Bax and cleaved caspase-3, and a decrease in Bcl-2 expression were observed after addition of PMA compared with the LPS+Ov-HMBOX1 group (Fig. 6C and D). By contrast, all of these effects aforementioned were reversed following co-transfection with si-CXCL10 (Fig. 6). Taken together, these data suggest that HMBOX1 may enhance the proliferation and inhibit the inflammation and apoptosis of LPS-induced hPDLSCs through the NF-κB/CXCL10 signaling axis.

**Discussion**

The homeobox family of protein contains ~300 gene members, most of which have been implicated in the regulation of embryonic development (22). In particular, HMBOX1 is ubiquitously expressed in human tissues and has been identified to be a novel transcription factor (6). HMBOX1 consists of a homeobox domain in the N-terminal region and an hepatocyte nuclear factor 1 domain at the C-terminus (7). In the present study, the expression levels of HMBOX1 were found to be downregulated in LPS-induced hPDLSCs. Therefore, the potential effects of HMBOX1 on the physiology of LPS-treated hPDLSCs were investigated by constructing an Ov-HMBOX1 plasmid and transfecting it into hPDLSCs. The cytotoxicity of LPS-induced hPDLSCs was mitigated following Ov-HMBOX1 transfection, which was accompanied by enhanced cell proliferation. In addition, the inflammation and apoptosis of LPS-induced hPDLSCs were alleviated following Ov-HMBOX1 transfection. The present study found also that increased HMBOX1 inhibited NF-κB activation in hPDLSCs in response to LPS. In addition to the potential involvement of NF-κB in the regulatory role of HMBOX1 in response to LPS, a previous study also showed that 5'AMP-activated protein kinase mediates the regulation of HMBOX1, which is associated with inflammation after EA.hy926 cells were subjected to LPS stimulation (9). Additionally, HMBOX1...
has been reported to be involved in cancer progression in an AKT-dependent manner, including osteosarcoma, lung cancer and liver cancer (23-25). However, whether MAPKs and AKT serve a role in the regulation of HMBOX1 upstream of inflammation and apoptosis in response to LPS require further study.

CXCL10 is an inflammatory cytokine that can be secreted by numerous cell types, including monocytes, endothelial cells, fibroblasts and mesenchymal cells (17). Previous studies reported that CXCL10 can regulate cell recruitment, migration and invasion (26,27). This subsequently attracted
the attention of researchers, who later proposed that the expression profile of CXCL10 can be used as a novel type of biomarker for acute lung injury (28). CXCL10 was also discovered to serve a regulatory role during the inflammatory response against hepatic ischemia and reperfusion injury, suggesting its potential for use in a novel therapeutic approach for this disease (29). In addition, a previous study reported a close association between CXCL10 expression and periodontitis (30).

The NF-κB signaling pathway is an extensively studied signaling pathway that can modulate the secretion of cytokines, chemokines and adhesion molecules (20). Activation of the NF-κB signaling pathway by osteopontin was found to increase bone destruction during periapical periodontitis (31). In addition, another study reported that NF-κB serve an important role in the pathogenesis of periodontitis (32). It was also previously reported that NF-κB signaling was activated in highly inflamed white
adipose tissues in obese rats with periodontitis compared with that in obese rats without periodontitis, suggesting a role for NF-κB in the pathogenesis of periodontitis (33). In the present study, following the treatment of PMA, an activator of the NF-κB signaling pathway, CXCL10 expression were reduced. In addition, hPDLSCs treated with PMA showed decreased cell viability and increased apoptosis, and increased levels of proinflammatory factors TNF-α, IL-6 and IL-1β compared with those in cells treated with LPS and transfected with Ov-HMBOX1 but without PMA treatment. However, the effects of inhibiting the NF-κB signaling pathway on CXCL10 expression require further study, which is a limitation of the present study. The NF-κB signaling pathway has also been implicated in the regulation of CXCL10. For example, the modulation of NF-κB was found to be mediated by COMM domain-containing 7 during anti-hepatocellular carcinoma therapy via CXCL10 upregulation (18). Furthermore, NF-κB signaling was revealed to regulate CXCL10 production in 4T1 breast cancer cells (34). Findings of the present study revealed that LPS-induced upregulation of CXCL10 expression was downregulated by Ov-HMBOX1 transfection, which was subsequently reversed by PMA treatment. These results support the hypothesis that HMBOX1 may regulate the physiology of LPS-induced hPDLSCs through the NF-κB/CXCL10 signaling axis. Furthermore, CXCL10 knockdown reversed the PMA-induced inhibition of cell proliferation whilst reducing the PMA-induced production of inflammatory cytokines and apoptosis in these cells.

In conclusion, to the best of our knowledge, the present study is the first to provide evidence to suggest that HMBOX1 overexpression can attenuate LPS-induced hPDLSC injury by downregulating CXCL10 expression through the NF-κB signaling pathway. This may provide a novel insight into the development of targeted treatment options for periodontitis in the future.
Figure 6. HMBOX1 blunts the inflammation and apoptosis of LPS-induced hPDLSCs through the NF-κB/CXCL10 axis. After PMA treatment, (A) the expression of inflammatory factors IL-6, TNF-α and IL-1β was measured by western blotting, whilst (B) the secretion of inflammatory factors IL-6, TNF-α and IL-1β was measured by ELISA. After PMA treatment, (C) apoptosis was measured using TUNEL, whereas (D) the expression of apoptosis-related proteins Bcl-2, Bax and caspase 3 in LPS-induced hPDLSCs transfected with Ov-HMBOX1 and si-CXCL10 was measured by western blotting. ***P<0.001 vs. control; ##P<0.01, ###P<0.001 vs. LPS+Ov-NC+si-NC; ∆P<0.05, ∆∆P<0.01, ∆∆∆P<0.001 vs. LPS+Ov-HMBOX1+si-NC; @@P<0.01, @@@P<0.001 vs. LPS+Ov-HMBOX1+PMA+si-NC.

hPDLSCs, human periodontal ligament stem cells; HMBOX1, Homeobox containing 1; LPS, lipopolysaccharide; Ov, overexpression; NC, negative control; CXCL10, C-X-C motif chemokine ligand 10; PMA, phorbol 12-myristate 13-acetate; si, small interfering.
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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MN, HL, PL and PD conceived and designed the study, performed the experiment, collected, analyzed and interpreted the data and revised the manuscript. MN wrote the manuscript. All authors read and approved the final manuscript. MN and PD confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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