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Sesamin suppresses macrophage-derived chemokine expression in human monocytes *via* epigenetic regulation

Chong-Chao Hsieh,†[a] Chang-Hung Kuo,†[bcd] Hsuan-Fu Kuo,[e] Yen-Shan Chen,[bc] Shih-Ling Wang,[cf] David Chao,[f] Min-Sheng Lee‡[bc] and Chih-Hsing Hung‡*[bcgh]

Background: Chemokines play important roles in the pathogenesis of asthmatic inflammation. Sesamin, a class of phytoestrogen isolated from sesame seed *Sesamum indicum*, is recently regarded as an anti-inflammatory agent. However, the effects of sesamin on asthma-related chemokines are unknown. To this end, we investigated the effects of sesamin on the expression interferon-γ-inducible protein-10 (IP-10/CXCL10), macrophage-derived chemokine (MDC/CCL22), growth-related oncogene-α (GRO-α/CXCL1) and tumor necrosis factor (TNF)-α in human monocytes. *Methods*: Cells were pretreated with sesamin before lipopolysaccharide (LPS) stimulation. IP-10, MDC, GRO-α and TNF-α were measured by ELISA. Involved receptors and intracellular signaling were investigated by receptor antagonists, pathway inhibitors, western blotting and chromatin immunoprecipitation. *Results*: Sesamin suppressed LPS-induced MDC in THP-1 and human primary monocytes. Sesamin suppressed LPS-induced IP-10 in THP-1 cells, but not human primary monocytes. Sesamin had no effects on LPS-induced GRO-α and TNF-α expression in THP-1 and human primary monocytes. The suppressive effect of sesamin on MDC was reversed by the estrogen receptor (ER) and peroxisomal proliferator-activated receptor (PPAR)-α antagonists. Sesamin suppressed LPS-induced phosphorylation of mitogen-activated protein kinase (MAPK)-p38 and nuclear factor kappa B (NFκB)-p65. Sesamin suppressed histone H3/H4 acetylation in the MDC promoter region. *Conclusion*: Sesamin suppressed LPS-induced MDC expression *via* the ER, the PPAR-α, the MAPK-p38 pathway, the NFκB-p65 pathway and the epigenetic regulation. Sesamin may have therapeutic potential in preventing and treating asthma.

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Introduction

Asthma is a chronic inflammatory airway disease which affects people of all ages throughout the world. Important characteristics of asthma are airway inflammation, airway remodeling and bronchial hyperresponsiveness. Both innate (neutrophils, eosinophils, basophils, mast cells and monocytes) and adaptive immune systems (particularly the predominant T help (Th) cell type 2 immune response) mediate these typical features.[1] Chemokines are 8–15 kDa chemotactic proteins produced by many immune and non-immune cells, with particularly important roles in asthma, including chemo-attraction of inflammatory cells, Th1/Th2 cell differentiation and activation, airway remodeling, and airway hypersensitivity.[2] Macrophage-derived chemokine (MDC/CCL 22) is a Th2-related chemokine recruiting CC chemokine receptor (CCR) 8- and CCR4-bearing Th2 cells in allergen-challenged inflammation,[3] and the levels of MDC in asthmatic patients are increased.[4] Interferon-inducible protein 10 (IP-10/CXCL10), a Th1-related chemokine, contributes greatly to inflammation and hyperreactivity in asthmatic airways,[5] and also mediates the late-phase reaction of airways in response to allergen.[6] In severe or refractory phenotype of asthma, neutrophil recruitment into the airway is a typical feature and is reported as a marker for severe or refractory asthma.[7] Tumor necrosis factor α (TNF-α), a pleiotropic pro-inflammatory cytokine, can recruit neutrophils

[a]*Division of Cardiovascular Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[b]*Department of Pediatrics, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan*
[c]*Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No.100, Tz-You 1st Road, Kaohsiung 807, Taiwan. E-mail: pedhung@gmail.com; Tel: +886-7-3121101-6506*
[d]*Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e]*Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[f]*Department of Biological Science, National Sun Yat-sen University, Kaohsiung, Taiwan*
[g]*Department of Pediatrics, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan*
[h]*Department of Pediatrics, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
† Chong-Chao Hsieh and Chang-Hung Kuo contributed equally to this work.
‡ Min-Sheng Lee and Chih-Hsing Hung contributed equally to this work.

and is recently regarded as a useful biomarker in refractory asthma.[8] Growth-related oncogene alpha (GRO-α/CXCL1), a CXC chemokine, is majorly involved in chemoattraction of neutrophil into airways, and plays an important role in pathogenesis of severe or refractory asthma.[9] As compared to normal controls, the number of bronchial subepithelial cells expressing GRO-α is greater in patients with severe exacerbation of asthma.[10] Recently, chemokines and their receptors have become potential targets for the treatment of asthma.

Sesame oil isolated from the sesame seeds (*Sesamum indicum*) contains lots of lignans, such as sesamin, sesamolin, sesaminol and sesamol, which have been shown to exhibit a variety of activities. Sesamin, a class of phytoestrogens, is the most abundant lignan in sesame seed oil. Recent studies reported that these sesame lignans have multiple pharmacological activities, including cholesterol- and lipid-lowering effects,[11] antioxidative effects,[12] and anti-inflammatory activities. However, whether these sesame lignans have regulatory effects on allergy and asthma-related inflammation is unknown.

Recently an important development in understanding the influence of chromatin on gene regulation has suggested that DNA methylation and histone modification, the "epigenetic marks", lead to the recruitment of protein complexes that regulate transcription which affects gene expression.[13] Asthma is characterized by the increased expression of multiple inflammatory genes, which can be epigenetically regulated by core histone modification. Histone acetylation is an important modification affecting gene transcription and is controlled by the action of histone acetyltransferase (HAT) and deacetylase (HDAC).[13] In bronchial biopsies and alveolar macrophages isolated from the bronchoalveolar lavage of asthmatic patients, the HAT activity is markedly increased and the HDAC activity is reduced, which favors increased inflammatory gene expression.[14] Some anti-asthmatic medications, such as corticosteroid and theophylline, can exert their anti-inflammatory effects by regulating HAT or HDAC activity.[14] In addition to histone acetylation, modifications on histones with trimethylation at H3K4, H3K36 and H3K79 are also associated with gene activation,[13] and these modifications are usually carried out by a variety of histone acetyltransferases or methyltransferases.[15] Recently, histone modification has become a novel target for anti-asthmatic drug development.[14] In our previous study, we have shown that some potential candidates for asthma treatment can regulate the expression of two important asthmatic-related chemokines *via* epigenetic regulation in human immune cells.[16,17]

In the present study, we investigated the effect of sesamin on the production of proinflammatory cytokine TNF-α, Th1-related chemokine IP-10, Th2-related chemokine MDC and neutrophil chemoattractant GRO-α in human monocytes and also explored the detailed mechanism including epigenetic regulation.

Materials and methods

Cell preparation

The human monocytic cell line, THP-1 (American Type Culture Collection, Rockville, MD), was cultured in RPMI 1640 medium (Sigma-Aldrich, St. Louis, MO) supplemented with 10% fetal bovine serum, 100 U mL^{-1} of penicillin, and 100 μg mL^{-1} of streptomycin at 37 °C with 5% CO_2 in a humidified incubator. THP-1 cells were centrifuged and resuspended in fresh medium in 24-well round-bottom plates at a concentration of 2×10^5 mL^{-1} for 24 h before experimental use. THP-1 cells were pretreated with sesamin (10^{-8} to 10^{-5} M; Sigma-Aldrich), 1 h before LPS (0.2 μg mL^{-1}; *Escherichia coli*-derived; Sigma-Aldrich) stimulation. Cell supernatants were collected 6, 24 and 48 h after LPS stimulation. To investigate the involved receptors, the cells were pretreated with estrogen receptor (ER) antagonist ICI182780 (Sigma Aldrich), aryl hydrocarbon receptor (AhR) antagonist CH-223191 (Albiochem, San Diego, CA), peroxisome proliferator-activated receptor (PPAR)-α antagonist GW6741 or PPAR-γ antagonist GW 9662 (Cayman Chemical, Ann Arbor, MI) 1 h before sesamin treatment, and then stimulated with LPS 2 h after sesamin treatment. To investigate the cell signaling, the cells were pretreated with IκB kinase (IKK) inhibitor BAY 117085 (Calbiochem, Cambridge, MA), or mitogen-activated protein kinase (MAPK)-p38 inhibitor (SB203580), ERK inhibitor (PD98059), or JNK inhibitor (SP600125) (Cayman Chemical) 1 h before sesamin treatment, and then stimulated with LPS 2 h after sesamin treatment.

To investigate the effect of sesamin on human primary monocytes, the study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital. After getting informed consents, peripheral blood samples were obtained from healthy subjects who had no personal or family history of allergic diseases ($n = 5$). Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation (Lymphoprep, Oslo, Norway), and human primary monocytes were isolated from PBMC by magnetic bead sorting with anti-CD14 monoclonal antibody (Miltenyi Biotec, Bergisch Gladbach, Germany). The purity of isolated monocytes was >95%.

Cell viability assay

THP-1 cells were incubated with sesamin at 10^{-5} M or vehicle solution for 2 h and were stimulated with LPS for 48 h. Cell viability was examined using the CytoScan WST-1 Cell Proliferation Assay (G-Biosciences, Maryland Heights, MO) according to the instruction of the manufacturer. The cell viability in each group was expressed as a percentage of the control group.

Enzyme-linked immunosorbent assay (ELISA)

The levels of TNF-α, MDC, IP-10 and GRO-α in the cell supernatants were measured using the commercially available ELISA assay (R & D system, Minneapolis, MN) following the manufacturer's instruction.

Western blotting

After treatment for 2 h with or without sesamin (10^{-5} M), the cells were stimulated with LPS (0.2 μg mL^{-1}) for 1 h and were lysed with equal volumes of ice-cold 150 μL lysis buffer. After centrifugation at 13 000 × *g* for 15 min, cell lysates were analyzed by western blotting with anti-MAPK/anti-phospho-MAPK (p38, ERK and JNK) antibodies and anti-p65/anti-phospho-p65 antibodies (Santa Cruz Biotechnology, Santa Cruz, CA).

Immunoreactive bands were visualized using horseradish peroxidase-conjugated secondary antibody and an enhanced chemiluminescence system (Amersham Pharmacia Biotech, Sunnyvale, CA).

Chromatin immunoprecipitation assay (ChIP)

ChIP was performed as per our previously published studies.[16,17] Briefly, cells (10^6 per well) were treated with 1% formaldehyde for 10 min at room temperature, followed by sonication of DNAs and immunoprecipitation of chromatins overnight with antibodies for acetylated H3 and H4 as a marker of gene silencing,[13] and with antibodies for CREB-binding protein (CBP) and p300. All antibodies for the ChIP assay were purchased from Upstate Biotechnology Company (Upstate Biotechnology, Waltham, MA). Immune complexes were collected using a protein A slurry (Invitrogen, Carlsbad, CA), and the DNA from the immune complex was quantified using a designed primer for the proximal promoter regions of the MDC.[16] PCRs were run on the ABI 7700 Taqman thermocycler (Applied Biosystems, Foster City, CA). The relative intensities of the amplified products were normalized to the input DNAs.

Statistical analysis

All data are presented as mean ± SD. For multiple comparisons in the experiments, data were analysed using one-way analysis of variance, followed by Dunnett's test. Intergroup comparisons were performed using unpaired Student's *t*-tests. Differences in intensities of PCR-amplified products in the ChIP assay, and differences of densitometry in western blotting were analyzed using paired Student's *t* test. *P* values less than 0.05 were considered significant.

Results

Sesamin suppressed MDC expression in THP-1 cells and human primary monocytes

Fig. 1 reveals that sesamin suppressed LPS-induced MDC (the Th2-related chemokine) expression in THP-1 cells in a dose-dependent and time-dependent manner (10^{-6} and 10^{-5} M after 24 and 48 h of LPS stimulation; Fig. 1A) and also suppressed LPS-induced IP-10 (the Th1-related chemokine) expression, to a lesser extent, in THP-1 cells in a time-dependent manner (10^{-6} and 10^{-5} M after 48 h of LPS stimulation; Fig. 1B). However, sesamin had no effect on TNF-α (the proinflammatory cytokine) and GRO-α (the neutrophil chemoattractant) expressions in THP-1 cells (Fig. 1C and D). Similarly, sesamin suppressed LPS-induced MDC in human primary monocytes in a dose-dependent and time-dependent manner (10^{-6} and 10^{-5} M after 24 and 48 h of LPS stimulation; Fig. 2A). However, sesamin had no effect on LPS-induced IP-10 expression in human primary monocytes (Fig. 2B). Sesamin had no effect on MDC, IP-10, TNF-α and GRO-α after 6 h of LPS stimulation in THP-1 and human primary monocytes (data not shown).

Sesamin had no cytotoxic effect on THP-1 cells

Next we verified whether the suppressive effect of sesamin on LPS-induced MDC expression was due to the cytotoxic effect of sesamin on THP-1 cells. As shown in Fig. 3, sesamin (10^{-6} and 10^{-5} M) had no effect on the cell viability of THP-1 cells.

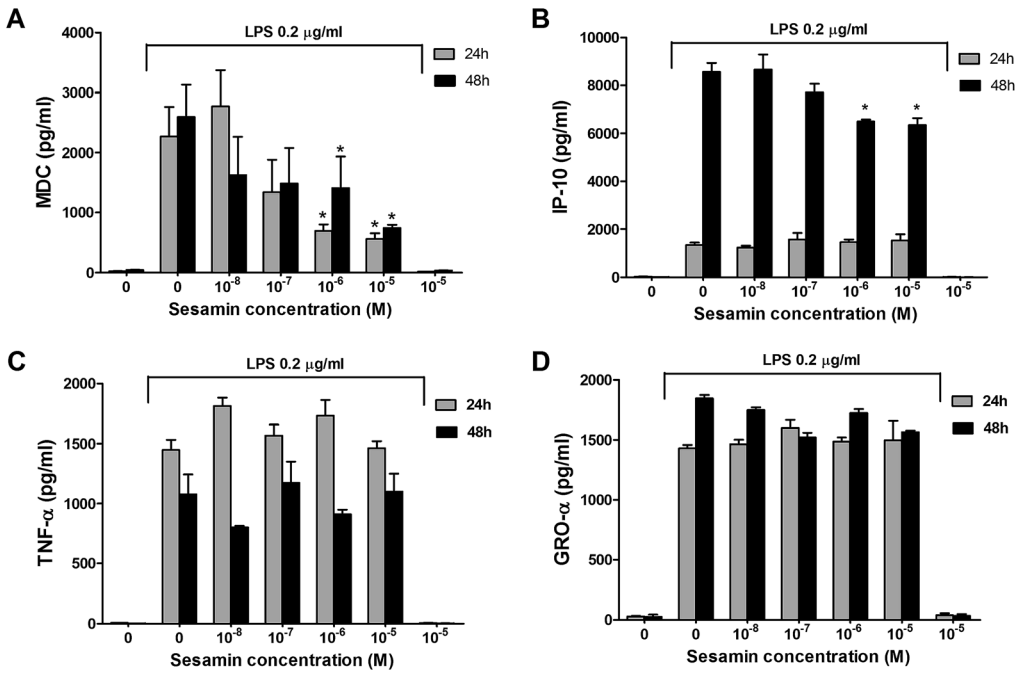

Fig. 1 Sesamin suppressed MDC and IP-10 expression in THP-1 cells. THP-1 cells were pretreated with sesamin for 2 h and then were stimulated with LPS for 24 and 48 h. Sesamin (10^{-6} to 10^{-5} M) suppressed (A) MDC at 24 and 48 h, and (B) IP-10 at 48 h. However, sesamin had no effect on (C) TNF-α and (D) GRO-α expression in THP-1 cells. Result presented the mean ± SD of six independent experiments. *, $P < 0.05$ compared with vehicle plus LPS-treated cells.

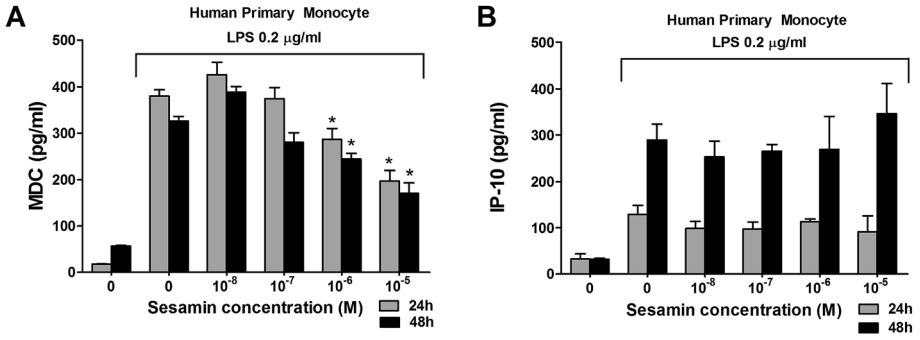

Fig. 2 Sesamin suppressed MDC in human primary monocytes. Human primary monocytes were pretreated with sesamin for 2 h and then were stimulated with LPS for 24 and 48 h. Sesamin (10^{-6} to 10^{-5} M) suppressed (A) MDC at 24 and 48 h but had no effect on (B) IP-10 expression in human primary monocytes. Result presented the mean ± SD of five independent experiments. *, $P < 0.05$ compared with vehicle plus LPS-treated cells.

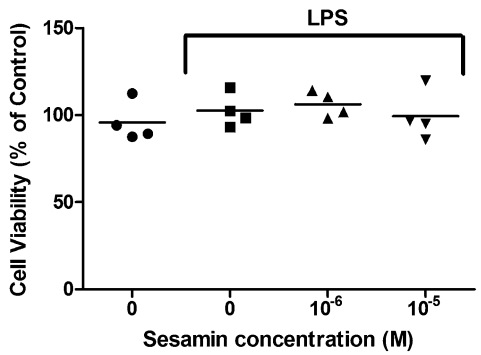

Fig. 3 Sesamin had no effect on cell viability in THP-1 cells. THP-1 cells pretreated with sesamin at 10^{-5} M or vehicle solution for 2 h and were stimulated with LPS for 48 h. The cell viability in each group was expressed as a percentage of the control group. Sesamin had no effect on cell viability in THP-1 cells. Four independent experiments were performed.

Sesamin suppressed LPS-induced MDC expression *via* the ER and PPAR-α

Natural products can exert their physiological effects *via* the estrogen receptor (ER; such as phytoestrogens), the aryl hydrocarbon receptors (AhR; such as polyphenols) or peroxisome proliferator-activated receptors (PPARs; such as some natural lipid metabolism regulators). Next we investigated whether sesamin suppressed LPS-induced MDC expression *via* these receptors. As shown in Fig. 4, ER antagonist ICI 182780 and PPAR-α antagonist reversed the suppressive effect of sesamin on LPS-induced MDC expression (Fig. 4A and B). However, PPAR-γ antagonist or AhR antagonist had no effect on the suppressive effect of sesamin on LPS-induced MDC expression (Fig. 4B and C). These data suggested that sesamin suppressed LPS-induced MDC expression *via* the ER and PPAR-α.

Sesamin suppressed LPS-induced MDC expression *via* the MAPK-p38 and the NFκB-p65 pathway

LPS can activate the MAPK and the NFκB pathway in human monocytes, and we have previously reported that LPS induces MDC expression in human monocytes *via* the MAPK-p38/JNK pathway and the NFκB-p65 pathway.[18] Western blotting revealed that sesamin suppressed phosphorylation of MAPK-p38 expression but had no effect on MAPK-JNK/ERK expression (Fig. 5A). Sesamin also suppressed phosphorylation of p65 expression (Fig. 5B). Taken together, these data suggested that sesamin suppressed LPS-induced MDC expression *via* the MAPK-p38 and NFκB-p65 pathways.

Sesamin suppressed LPS-induced MDC expression *via* suppressing histone acetylation through inhibiting NFκB-associated acetyltransferase CBP

Epigenetic regulation by histone modifications can be one of the mechanisms of gene expression, and histone acetylation is a marker for gene activation.[13] We next examined whether the suppressive effect of sesamin on LPS-induced MDC expression was through epigenetic regulation by histone modification. It has been reported that the activation of NFκB recruits acetyltransferases such as CBP/p300 and subsequently leads to histone acetylation.[19] Because sesamin suppressed LPS-induced MDC expression *via* suppressing NFκB-p65 expression (Fig. 5B), we next investigated whether sesamin modulates histone acetylation. The ChIP assay revealed that sesamin suppressed LPS-induced histone H3 and H4 acetylation in the MDC promoter region. We next examined whether sesamin modulates NFκB-associated acetyltransferases CBP and p300. We found that sesamin suppressed the recruitment of CBP, but not p300 in the MDC promoter region (Fig. 6B).

Discussion

In the present study we demonstrated the effects of sesamin on the expression of allergy and asthma-related cytokine (TNF-α) and chemokines (MDC, IP-10, GRO-α) in LPS-stimulated human monocytes. Although sesamin did not modulate the expression of IP-10, GRO-α and TNF-α, sesamin significantly suppressed LPS-induced Th2-related chemokine MDC expression in human monocytes. In addition, we also provided evidence for the detailed mechanisms, including the involved receptors, the MAPK/NFκB pathways and the epigenetic regulation, for the suppressive effect of sesamin on LPS-MDC expression in

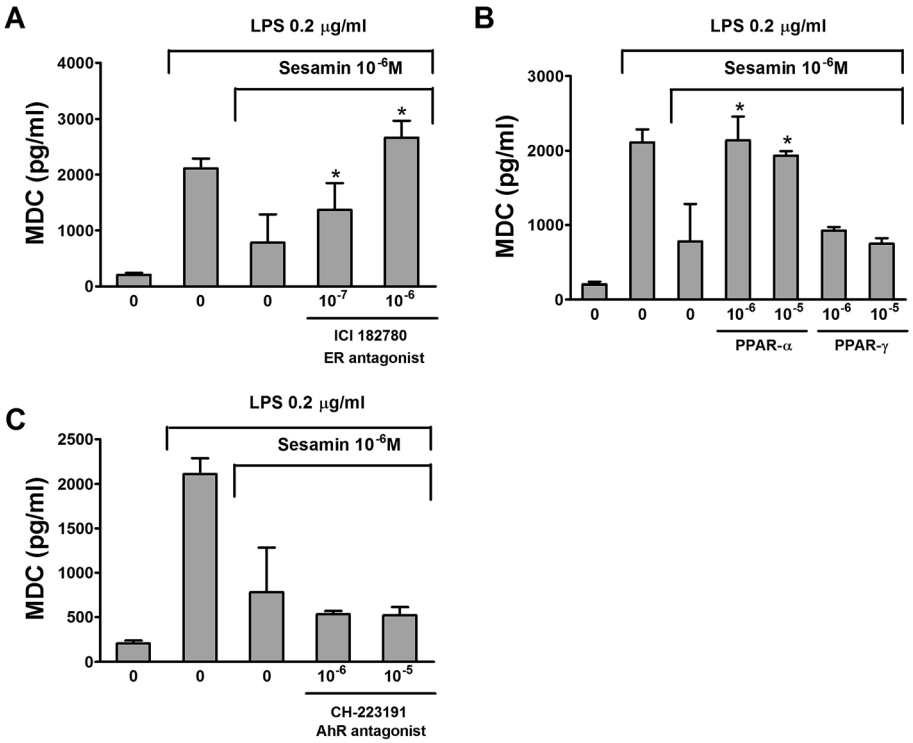

Fig. 4 Sesamin suppressed LPS-induced MDC expression *via* the ER and PPAR-α. THP-1 cells were pretreated with receptor antagonists for 1 h before sesamin treatment for 2 h, and then stimulated with LPS for 24 h. Pretreatment with (A) ICI 182780 (the ER antagonist) and (B) GW 6741 (the PPAR-α antagonist) reversed the suppressive effect of sesamin on LPS-induced MDC expression. However, (B) GW 9662 (the PPAR-γ antagonist) and (C) CH-223191 (the AhR antagonist) had no effect on the suppressive effect of sesamin on LPS-induced MDC expression. Result presented the mean ± SD of six independent experiments. *, $P < 0.05$ compared with sesamin plus LPS-treated cells.

monocytes. The concentrations of sesamin required to suppress chemokine expression in our study were similar to those reported to inhibit expression of other inflammatory cytokines[20] and suppress proliferation of tumor cells.[21] In animal[22] and human[23] studies, it is reported that under a safe oral dose, sesamin and its metabolites were detected in the blood plasma at concentrations over 1 μM, and the concentration of the primary metabolite SC-1 can even be greater than 10 μM. These novel findings suggest that as a phytoestrogen with anti-inflammatory effects, sesamin also has an immunomodulatory effect on the expression of allergy and asthma-related chemokine in human monocytes.

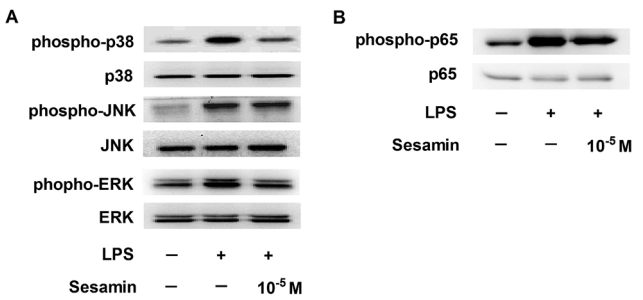

Fig. 5 Sesamin suppressed LPS-induced MDC expression *via* the MAPK-p38 and the NFκB-p65 pathways. THP-1 cells were pretreated with sesamin for 2 h and were stimulated with LPS for 1 h. Cell lysates were analyzed using western blotting. (A) Sesamin suppressed LPS-induced phosphorylation of MAPK-p38 expression, but not JNK or ERK. (B) Sesamin suppressed LPS-induced phosphorylation of NFκB-p65 expression. One experiment representative of three independent western blotting analyses is shown.

Chemokines play an important role in the pathogenesis of allergic reaction and asthma and have become potential targets for the treatment of asthma. As a Th2-related chemokine, MDC recruiting Th2 cells mediate inflammatory reaction in response to allergen.[3] The levels of MDC in asthmatic patients are increased in plasma and breath condensate,[4] and can be decreased after inhaled corticosteroid[4] and ketotifen[24] treatment. In the present study, sesamin suppressed MDC expression in LPS-stimulated human monocytes. The evidence may suggest the therapeutic potential of sesamin in preventing and treating asthma and allergic diseases by modulating the expression of Th2-related chemokine MDC. These findings deserve further studies to clarify the *in vivo* effects of sesamin in animal or clinical studies.

The findings in the present study that sesamin suppressed MDC expression support the current evidence for the anti-inflammatory effect of sesamin. The anti-inflammatory activities of sesamin are found in various types of cells, including macrophages, microglia cells and endothelial cells, with the inhibitory effects on the expression of nitric oxide,[25] IL-6/TNF-α,[20] and IL-8/adhesion molecules,[26,27] respectively. Sesamin also

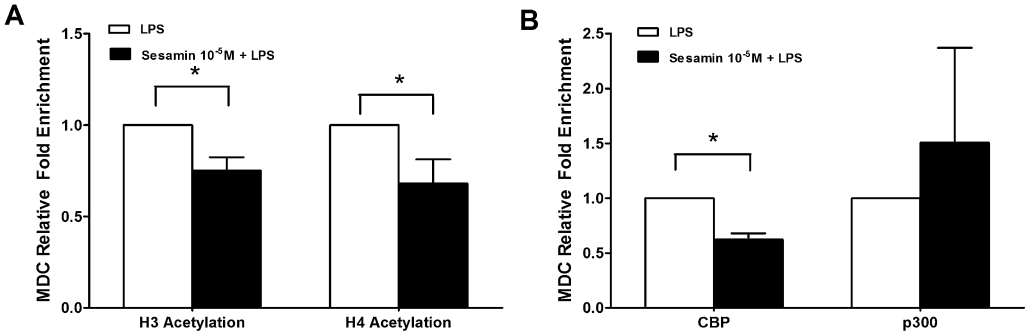

Fig. 6 Sesamin suppressed LPS-induced MDC expression *via* suppressing histone acetylation through inhibiting NFκB-associated acetyltransferase CBP. (A) Sesamin suppressed histone H3 and H4 acetylation at the MDC promoter region. (B) Sesamin suppressed NFκB-associated acetyltransferase CBP, but not p300, in the MDC promoter region. Result presented the mean ± SD of three independent experiments. *, $P < 0.05$ compared with vehicle plus LPS-treated cells.

inhibits the reaction of human monocytes to chemoattractants and subsequently attenuates inflammatory responses.[28] In animal models, sesamin prevents LPS-mediated shock by diminishing the LPS-induced interleukin-1β, prostaglandin E2, and thromboxane B2.[29] Sesamin increases the survival of mice after cecal ligation and puncture by increasing the IL-10 levels.[30] The present study is, to the best of our knowledge, the first report which reveals the effect of sesamin on allergy and asthma-related chemokines in human monocytes, adding further understanding to the modulatory effects of sesamin on immune cells.

The present study provided a detailed intracellular mechanism by which sesamin suppressed LPS-induced MDC in human monocytes. NFκB activation is responsible for many inflammatory gene expressions in airway cells from patients with asthma,[14] and has been shown to specifically bind to the proximal promoter region of MDC in LPS-stimulated immune cells, including B cells, DCs[31] and monocytes in our recently published work.[16] We have previously reported that LPS-induced MDC expression in monocytes is NFκB and MAPK-p38/JNK dependent.[18] In the present study, western blotting analyses revealed that sesamin suppressed LPS-induced phosphorylation of MAPK-p38 and NFκB-p65, suggesting that sesamin suppressed LPS-induced MDC expression *via* the MAPK-p38 and NFκB-p65 pathways. Interestingly and consistently, the suppressive effect of sesamin on MAPK-p38/NFκB pathways is also reported in microglia cells[20] and recently in human aortic endothelial cells.[27] It is known that the MAPK-p38 can regulate NFκB-dependent gene transcription by modulating activation of TATA box binding protein but not altering phosphorylation of the p65 subunit.[32] In the present study, sesamin may suppress LPS-induced MDC expression by its additive inhibition on both MAPK-p38/NFκB pathways.

Another important novel finding of the present study is that we provided, for the first time in the literature, an additional insight into the epigenetic regulation of sesamin. Modification on histone with acetylation is associated with gene activation,[13] and the acetylation levels in asthmatic patients are elevated by the increased activity of histone acetyltransferase and the decreased activity of histone deacetylase, favoring the increase of inflammatory gene expression.[14] Recently, histone modification has become a novel target for anti-asthmatic drug development and we have reported that some potent anti-asthmatic therapy can modulate the function of immune cells by histone modification in the promoter region of specific genes.[16,17] It is known that NFκB activation can interact with coactivator molecules, such as CBP and p300, which have intrinsic activity of acetyltransferase for histone acetylation.[19] In the present study, we found that sesamin suppressed LPS-induced H3 and H4 acetylation in the MDC promoter area, and the suppressive effect may be resulted from decreasing recruitment of the NFκB-p65-associated histone acetyltransferase CBP. These novel findings suggested that epigenetic regulation may be one of the important mechanisms by which phytoestrogens modulate chemokine expression in immune cells.

In conclusion, sesamin suppressed LPS-induced MDC expression in monocytes through the ER/PPAR-α, the MAPK-p38 pathway, the NFκB-p65 pathway and the epigenetic regulation by suppressing histone H3/H4 acetylation in the MDC promoter region through inhibiting NFκB-associated acetyltransferase CBP. The *in vitro* effects of sesamin on MDC expression deserve further investigation to verify its biological activity *in vivo* using a murine asthma model or clinical studies. Natural foods containing sesamin may benefit patients with allergy or asthma.

Conflict of interest

The authors declare no conflict of interest in relation to the work and the manuscript.

Acknowledgements

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