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FABP4 induces asthmatic airway epithelial barrier dysfunction via ROS-activated FoxM1

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ABSTRACT

Functional abnormal airway epithelial cells, along with activated inflammatory cells, resulting in chronic airway inflammation, are considered as the characteristic of asthma. Fatty Acid Binding Protein 4 (FABP4) takes part in glucose and lipid homeostasis, and also have an important role in allergic airway inflammation. However, whether FABP4 influence barrier function of airway epithelial cells is unknown. In vivo, a HDM-induced murine model of asthma was obtained to assessed airway inflammation and protein expression of E-cadherin and Forkhead Box M1 (FoxM1). In vitro, 16-HBE was cultured and was treated with hrFABP4, siFABP4, FABP4 inhibitor BMS, or FoxM1 inhibitor RCM-1. IL-4, IL-5, and IL-13 level was determined by ELISA. Transepithelial electrical resistance (TER), paracellular permeability and E-cadherin-special immunofluorescence were measured to value airway epithelial barrier function. Intracellular ROS production was determined by DCF-DA fluorescence. FABP4 inhibitor BMS alleviate airway inflammation and destruction of E-cad in allergic mouse. Treatment with HDM or hrFABP4 aggravated inflammatory response, damaged airway epithelial barrier, which could be inhibited by siFABP4 and BMS. Treatment with HDM or hrFABP4 also enhanced levels of FoxM1, and Inhibited FoxM1 suppressed HDM- and hrFABP4-induced inflammation and airway epithelial barrier dysfunction. In addition, H₂O₂ promoted FoxM1 expression, HDM and hrFABP4 induced-FoxM1 could be inhibited by NAC, leading to decreased inflammation and improved airway epithelial barrier. Upregulated ROS induced by FABP4 was of significance in activating FoxM1 leading to airway inflammation and epithelial barrier dysfunction.

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1. Introduction

Asthma, highly relevant to environmental factors such as pollutants and allergens, is a chronic airway inflammatory disease [1]. However, the underlying pathogenetic mechanism of asthma is still not fully understood. Increasing researches have revealed that numerous inflammatory cells including Th2 lymphocytes, neutrophils, eosinophils, are critical for the pathogenesis of asthma [2]. Accumulation of pro-inflammatory mediators, for example, IL-4, IL-5, IL-9, and IL-13, initiate and promote asthma's development [3], and the reactive oxygen species (ROS), which linked to a variety of cellular signaling cascades, is the most critical mediator that causes

respiratory inflammation [4]. In addition, the airway epithelial cells, act as a crucial barrier defense against inhaled harmful substances, is often injured in asthma patients [5]. Inhaled particles, as well as infiltrated inflammatory cells, working together to increase ROS, make the epithelial cells to be the first victim [6].

Fatty acid binding protein 4 (FABP4), also named as adipocyte P2 (aP2) or adipocyte-FABP (A-FABP), takes part in modulating various biological processes, such as inflammation, glucose and lipid homeostasis, by regulating lipid trafficking and responses in cells [7,8]. Previous studies have shown that FABP4, which mainly expressed in macrophages and adipocytes, was closely related to obesity, diabetes mellitus, cardiac dysfunction, ect [9,10]. However,

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the role of this protein in respiratory diseases has not been fully understood. Evidences gradually revealed that FABP4 involved in the pathological process of respiratory diseases. Shum's study [2] have shown that FABP4 expression in human bronchial epithelial cells (HBEs) was enhanced by Th2 cytokines IL-4 and IL-13, and lung inflammation and airway eosinophilia in allergic FABP4-deficient mouse was obviously ameliorated. Nevertheless, the regulatory mechanism of FABP4 in asthma is not yet to be fully understood. Recent studies have shown that FABP4^{-/-} macrophages diminished ROS production [11], and deficient FABP4 attenuates NF-kappaB signaling, reduced inflammatory cytokine secretion [12]. Thus, we surmised that FABP4 might induce inflammation via ROS in lung allergic responses.

FoxM1, a member of the forkhead box (FOX) transcription factor family, has an important role in cell-cycle progression [13,14]. Previous studies have shown that FoxM1 was closely related to human malignancies, as it was over-expressed in a number of carcinomas, like prostate, lung, liver, colon and kidney [15]. Whereas, some recent reports demonstrated that FoxM1 also has an important role in the development of respiratory diseases. Foxm1 is required for macrophage recruitment during lung inflammation [16] and deletion of FoxM1 reduced production of Th2 cytokines, alleviated lung inflammation in response to house dust mite (HDM) allergen [17].

Interestingly, there seem to be a potential links between FABP4, FoxM1 and ROS. As exogenous FABP4 treatment in MCF-7 cells enhanced levels of FoxM1 [18], and the expression of FoxM1 required ROS [19], we put forward the hypothesis that FABP4 influence barrier function of airway epithelial cells via ROS-activated FoxM1.

2. Materials and methods

2.1. Materials

Methacholine (Sigma-Aldrich, Shanghai, China), BMS, NAC, RCM1 (Robert Costa Memorial drug-1, 10 µM), HDM (ALK-Abello A/S, Alutard, Denmark), IL-4, IL-5, IL-13, IL-33, IFN-γ (all from the Affymetrix product line, eBiosciences), hrFABP4 (Biovendor, Brno, Czech Republic), siFABP4 (santa cruz, USA).

2.2. Animals

All experimental procedures were performed with approval of the Committee on the Ethics of Animal Experiments of Southern Medical University and were complied with the institutional animal ethics committee. BALB/c mice (male, 6-week old, 20–24 g) housed in specific pathogen-free housing under conventional barrier protection were purchased from Southern Medical University.

2.3. Animal treatment regimens

In this study, the BALB/c mice were anaesthetized by sevoflurane-anesthesia (Maruishi Pharmaceutical Co. Ltd.) and challenged with 10 ml phosphate-buffered saline (PBS), or HDM alone (400 U per mouse, instilled intratracheally –dose selected from a previous study [20]), or BMS (40 mg/kg/d oral gavage [21]) plus HDM (400 U per mouse). After challenge for 24 h, the enhance pause (Penh) was measured to evaluate bronchial hyper-responsiveness (BHR). Mice were placed in a barometric plethysmo-graphic chamber (Buxco Electronics, Troy, NY) and provoked with vehicle (PBS), followed by increasing concentrations of methacholine (6.25, 12.5, 25, 50, or 100 mg/ml) via a nebulizer (Buxco Electronics, Inc., Troy, NY) for 3 min [20].

2.4. Leukocyte counts in BALF

Bronchoalveolar lavage fluid (BALF) was collected to count and classify the inflammatory cell. The BAL was centrifuged the precipitate was stained with HE stain to permit differential leukocyte counts. The leukocyte classification was based on cellular staining characteristics and morphology.

2.5. HE staining

The lung histology of mice was fixed in 4% paraformaldehyde and embedded in paraffin. Paraffin sections were cut and conventional dewaxed before staining with HE for general histology and inflammatory cell counts.

2.6. Immunohistochemical staining

The lung histology was 4% paraformaldehyde-fixed, paraffin-embedded, and processed for staining. Then the tissue was incubated with anti-E-cadherin antibody (1:500 Santa Cruz Biotechnology), anti-FoxM1 antibody (1:1000 Abcam) and anti-FABP4 antibody (1:1000 Abcam) at 4 °C overnight followed by incubation with secondary antibody, at last stained with DAB and counterstained with hematoxylin.

2.7. Cytokines measurement by ELISA

IL-4, IL-5, and IL-13 level in lung tissue and in culture supernatant was determined with ELISA kit according to the manufacturer's instructions.

2.8. Intracellular ROS measurement

Intracellular ROS production was determined by an oxidation-sensitive probe, 2,7-dichlorofluoresceindiacetate (DCF-DA). Briefly, after treating with HDM or hrFABP4, with or without NAC, cells were incubated with 10 µmol/L DCF-DA for 30 min at 37 °C. And the DCF-DA fluorescence intensity was measured by a multiwell fluorescence scanner (SpectraMax M5/M5e, Molecular Devices, USA). DCF-DA fluorescence was measured at an excitation wavelength of 480 nm and an emission wavelength of 525 nm.

2.9. Cell culture and transfection

Human bronchial epithelial cells (16-HBE) were cultured in DMEM (Invitrogen) with 10% fetal bovine serum. Specific siRNA against FABP4 (siFABP4) (sc-43592, Santa Cruz Biotechnology) and optimal concentration human recombination FABP4 (hrFABP4) (Biovendor, Brno, Czech Republic) were selected. The Negative Control siRNA (sc-43592, Santa Cruz Biotechnology) was used as a silencing control. The cells were transfected using the Lipofectamine 2000 according to the manufacturer's instructions.

2.10. Western blot analysis

Cells were lysed with SDS lysis buffer supplemented with protease inhibitors. Total cell extracts were separated by SDS-PAGE and transferred to a polyvinylidene difluoride (PVDF) membrane. After blocking with 5% PBS, membranes were incubated with following antibodies: FABP4, FoxM1, E-cadherin. Membranes were incubated over night at 4 °C and then incubated with secondary antibody for 1 h at room temperature. Finally, the detection was performed with Odyssey infrared imaging (Li-Core Biosciences). All Western blots were repeated three times at least.

2.11. Transepithelial electrical resistance (TER) measurement

16-HBE cells were cultured in a 12-mm Transwell inserts and the TER was measured using Millicell-ERS (Millipore). The Transwell insert without cells was measured as blank control. The sample resistance was calculated from the total resistance subtracting the blank value.

2.12. Paracellular permeability assay

To determine airway epithelial barrier integrity, we used fluorescein isothiocyanate (FITC)-dextran 4000 Da to perform the following experiment. 16-HBE cells were cultured in 12-mm transwell inserts. Before the experiments, the lower chambers and upper chambers were replaced with fresh medium (1 mL and 250 μ L), and then added FITC-dextran (50 μ L) to the upper chamber. Then the transwell plates incubated at 37 °C for 3–4 h. The diffused FITC-dextran in the lower chamber (100 μ L/well) was transferred to a new black 96-well plate to measure the fluorescence intensity. The fluorescence was measured at an excitation wavelength of 480 nm and an emission wavelength of 525 nm.

2.13. Immunocytochemistry

Cells cultured on six-well culture plates were fixed with 3.7% formaldehyde in PBS at for 20 min. Then the cells were permeabilized with PBS containing 0.25% Triton® X-100 for 10 min and then blocked with 5% bovine serum albumin (BAS) for 30 min–1 h at room temperature. Next, the cells were incubated with anti-E-cadherin primary antibody overnight at 4 °C. Cells incubated with secondary antibody for 1 h at room temperature, and nuclei were stained with DAPI for 5 min.

2.14. Statistical analysis

All of the results are represented as the means values $\pm$ standard deviation. Significant differences were evaluated by ANOVA. $p < 0.05$ were considered statistically significant. All of the data were analyzed using SPSS 13.0®.

3. Result

3.1. FABP4 inhibitor BMS alleviate airway inflammation and destruction of E-cad in allergic mouse

Mouse sensitized with HDM were challenged with gradually increasing concentrations of methacholine aerosol from 6.25 to 100 mg/m L. Enhance pause (Penh) was measured to evaluate bronchial hyperresponsiveness (BHR). We observed that the Penh value of the asthma group was significantly increased, whereas, treatment with BMS, a FABP4 inhibitor, was decreased (Fig. 1 A). Numerous inflammatory cells including Th2 lymphocytes, neutrophils, eosinophils, as well as cytokines, like IL-4, IL-5, take part in the pathogenesis of asthma [2]. We also observed that IL-4, IL-5, and IL-13 were significantly enhanced in the asthma group, which could be inhibited by treatment with BMS (Fig. 1B–D). Besides, Total inflammatory cells, neutrophils, and eosinophils in bronchoalveolar lavage fluid (BALF) were also enhanced in allergic mouse, while all these were decreased in response to BMS (Fig. 1 F, H). On the other hand, macrophage in BALF was significantly reduced in the asthma group compared to the group treatment with BMS (Fig. 1 G). Besides, HE staining showed that a large amount of inflammatory cells were infiltration in the asthma group, which were remarkably suppressed after treated with BMS (Fig. 1 I, J). Allergens enter the body and then induce secretion of IgE, thus

elevated IgE in serum is the best indication of allergic disease. In our study, we observed that IgE in allergic mouse was significantly enhanced while that was decreased in response to BMS (Fig. 1 E). Studies have shown that E – cadherin protein related to the airways barrier function injury in the asthma patients [22]. Immunohistochemical staining demonstrated that the expression of E-cadherin in asthma group was decreased with disordered cell arrangement, while treatment with BMS improved the expression of E – cadherin and cell arrangement was partly back to normal (Fig. 1 K).

3.2. Knocked-down or inhibited FABP4 suppressed HDM-induced inflammation and airway epithelial barrier dysfunction in 16-HBE

The most appropriate concentration of human recombination FABP4 (hrFABP4) (Fig. 2 A) and the most effective siFABP4 (Fig. 2 B) were selected to be applied to the following experiments. To observe the relationship between FABP4, inflammation and barrier function in vitro, we used human bronchial epithelial cells (16-HBE) to perform our experiments. Treatment with HDM resulted in a significantly increasement of IL-4, IL-5, and IL-13. Similar to HDM, hrFABP4 also induced these inflammatory factors, though was not as obvious as HDM. However, pre-treatment with FABP4 siRNA (siFABP4) and FABP4 inhibitor BMS attenuated HDM-induced inflammatory factors I secretion (Fig. 2 C). To evaluate the barrier function, transepithelial electrical resistance (TER) and paracellular permeability were measured. The TER values of 16-HBE cells were remarkably decreased in response to HDM, as well as hrFABP4, which were improved by pre-treatment with BMS and siFABP4 (Fig. 2 D). Furthermore, the permeability increased significantly after treating with HDM and hrFABP4, while exhibited an obviously decrease in the groups pre-treated with BMS and siFABP4 followed by HDM treatment (Fig. 2 E). What's more, E-cadherin -specific immunofluorescence staining was utilized to assess the barrier function within 16-HBE cells. The E-cadherin -specific fluorescence distributed around cell-to-cell was reduced after challenge with HDM and hrFABP4, yet was ameliorated contributed to pre-treatment with BMS and siFABP4 (Fig. 2 F). However, the protein level of E-cadherin in 16-HBE cells had neither significant difference in the groups treating with HDM or hrFABP4, nor in the groups treating with BMS or siFABP4 (Fig. 2 G).

3.3. Inhibited FoxM1 suppressed HDM and hrFABP4-induced inflammation and airway epithelial barrier dysfunction in 16-HBE

Recent reports demonstrated that FoxM1 also has an important role in the development of respiratory diseases [16,17]. Our in vivo experiments, FoxM1-specific immunohistochemical staining and western blotting, both demonstrated that FoxM1 was markedly increased in the asthma group, whereas recovered in the BMS-pretreatment group (Fig. 3 A, B). In vitro, we found that treatment with HDM and hrFABP4 resulted in an obvious increasement of FoxM1 expression, which was inhibited by pre-treatment with FABP4 inhibitor BMS and siFABP4 (Fig. 3 C). However, the increasement of FoxM1, induced by HDM and hrFABP4, was abolished by pre-treatment with FoxM1 inhibitor RCM-1 (Fig. 3 D). Similarly, the secretion of IL-4, IL-5, and IL-13 induced by HDM and hrFABP4, were significantly decreased in response to RCM-1 (Fig. 3 E). Furthermore, comparing with the groups treated with HDM and hrFABP4, the groups pretreated with RCM-1 contributed to higher TER, lower permeability, as well as stronger E-cadherin -specific fluorescence expression (Fig. 3 F, G, H). However, the protein expression of E-cadherin was still no difference after treatment with HDM, hrFABP4 and RCM-1 (Fig. 3 I).

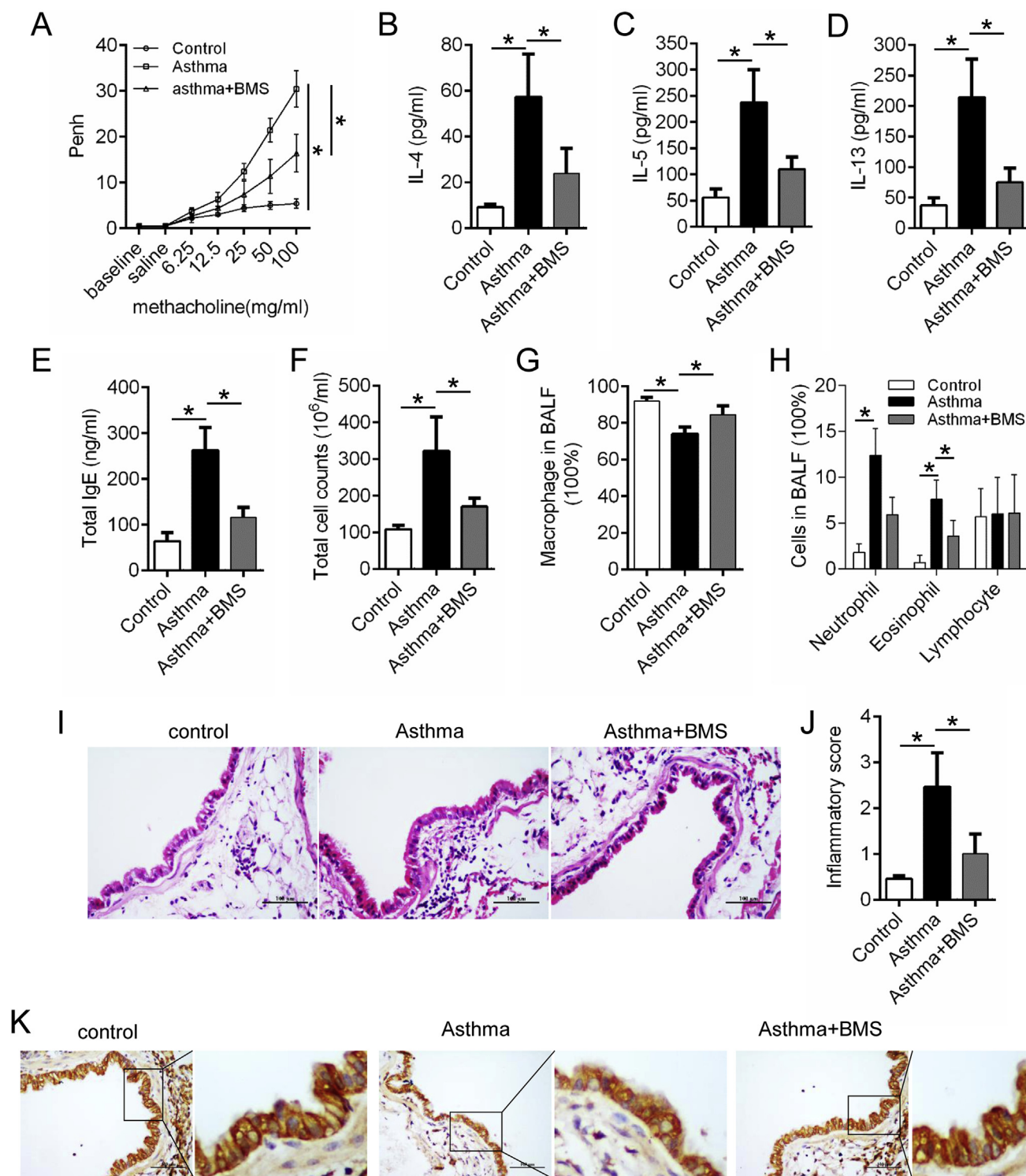


Fig. 1. FABP4 inhibitor BMS alleviates airway inflammation and destruction of E-cadherin in allergic mice. (A) The enhance pause (Penh) was measured followed by increasing concentrations of methacholine (6.25, 12.5, 25, 50, or 100 mg/ml). (B–D) IL-4, IL-5, and IL-13 level in lung tissue was determined by ELISA. (F) Total inflammatory cells in BALF were counted. (G, H) Inflammatory cells in BALF were counted classified. (I, J) The lung histology of mice was stained with HE for general histology and inflammatory score counting. (K) Immunohistochemical staining of E-cadherin was shown.

3.4. HDM and hrFABP4 activated FoxM1 via ROS

As demonstrated above, FoxM1, activated by HDM and hrFABP4, took part in the development of inflammation and airway damage. However, the molecular mechanism between FABP4 and FoxM1 was unclear. We found that treatment with HDM and hrFABP4 enhanced

the production of ROS, which could be inhibited by treating with ROS scavenger NAC (Fig. 4 B, C). In addition, treating with BMS and siFABP4 has a similar effect with NAC in inhibiting ROS (Fig. 4 B, C). Furthermore, FoxM1, activated by H₂O₂, could be also activated by HDM and hrFABP4 and was relieved by pre-treating with NAC (Fig. 4 A, D). Besides, comparing with the groups treated with HDM and

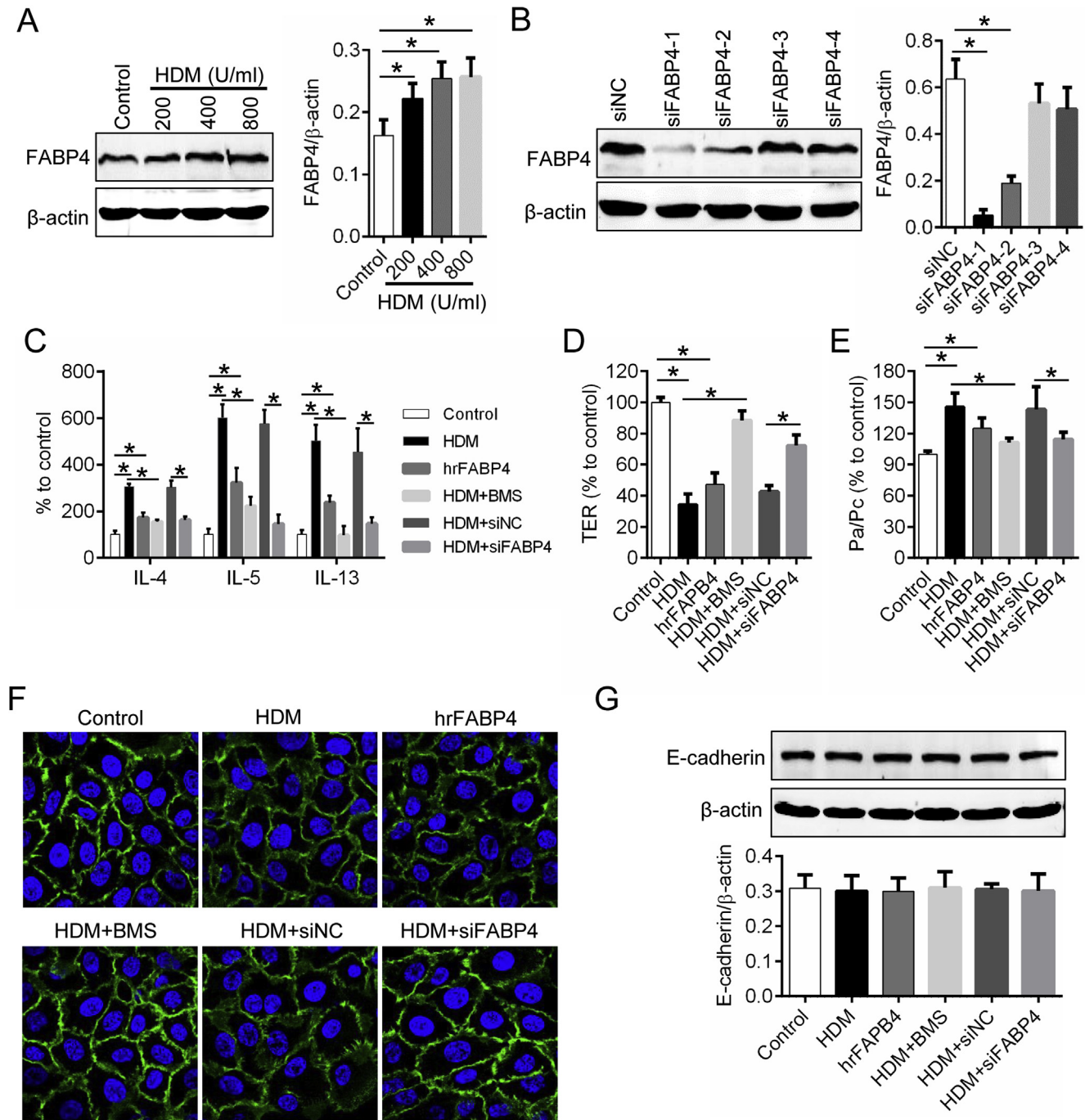


Fig. 2. Knocked-down or inhibited FABP4 suppressed HDM-induced inflammation and airway epithelial barrier dysfunction in 16-HBE. (A) Increasing concentrations (200, 400, and 800 ng/ml) of hrFABP4 were transfected to 16-HBE and the protein level FABP4 was assessed by Western blot. (B) IL-4, IL-5, and IL-13 level in culture supernatant was determined by ELISA. Airway epithelial barrier function was valued by transepithelial electrical resistance (TER) (D) and paracellular permeability (E). The expression of E-cadherin in 16-HBE was assessed by immunofluorescence (F) and Western blot (G).

hrFABP4, the groups pretreated with NAC contributed to depressed secretion of IL-4, IL-5, and IL-13, higher TER, reduced permeability, as well as stronger E-cadherin-specific fluorescence expression (Fig. 4 E, F, G, H), though there was no difference in these groups in the protein expression of E-cadherin (Fig. 3 I).

4. Discussion

In our study, we identified a novel potential pathway in bronchial epithelium in allergic airway disease. We present evidence

that FABP4 plays an important role in airway inflammatory cytokine production and airway barrier integrity. Besides, upregulated ROS induced by FABP4 is of significance in activating FoxM1 in airway epithelial barrier dysfunction.

Airway epithelium is the first barrier defense against harmful substances, which leading to disruption of the epithelial barrier [23]. Functional abnormal airway epithelial cells, along with activated inflammatory cells such as dendritic cells, Th2 cells, resulting in chronic airway inflammation, are considered as the characteristic of asthma [24]. Shum's study have demonstrated that FABP4

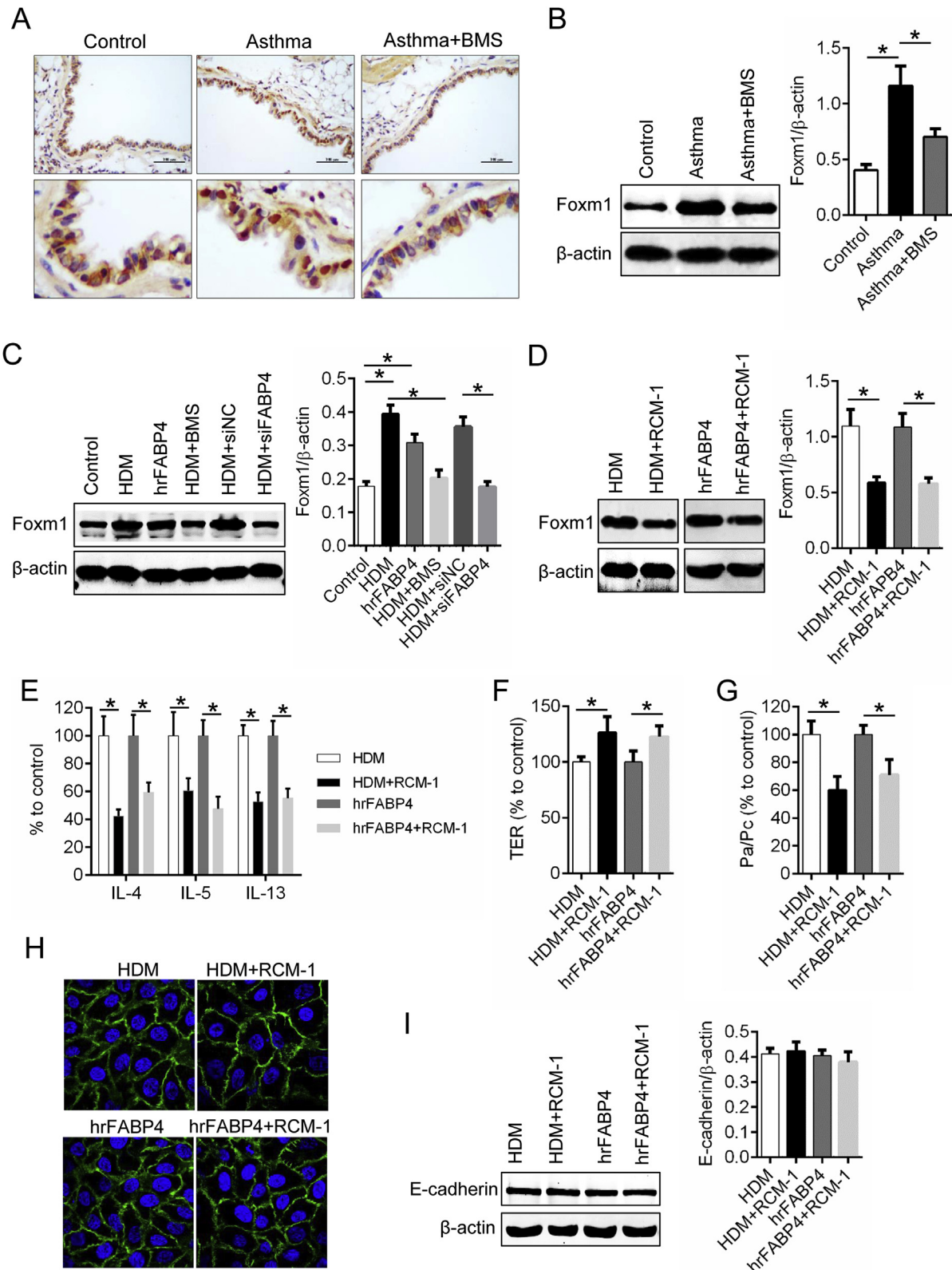


Fig. 3. Inhibited FoxM1 suppressed HDM- and hrFABP4-induced inflammation and airway epithelial barrier dysfunction in 16-HBE. The expression of FoxM1 in lung tissue was assessed by immunohistochemistry (A) and Western blot (B). (C, D) The expression of FoxM1 in 16-HBE was assessed by Western blot. (E) IL-4, IL-5, and IL-13 level in culture supernatant was determined by ELISA. Airway epithelial barrier function was valued by transepithelial electrical resistance (TER) (F) and paracellular permeability (G). The expression of E-cadherin in 16-HBE was assessed by immunofluorescence (H) and Western blot (I).

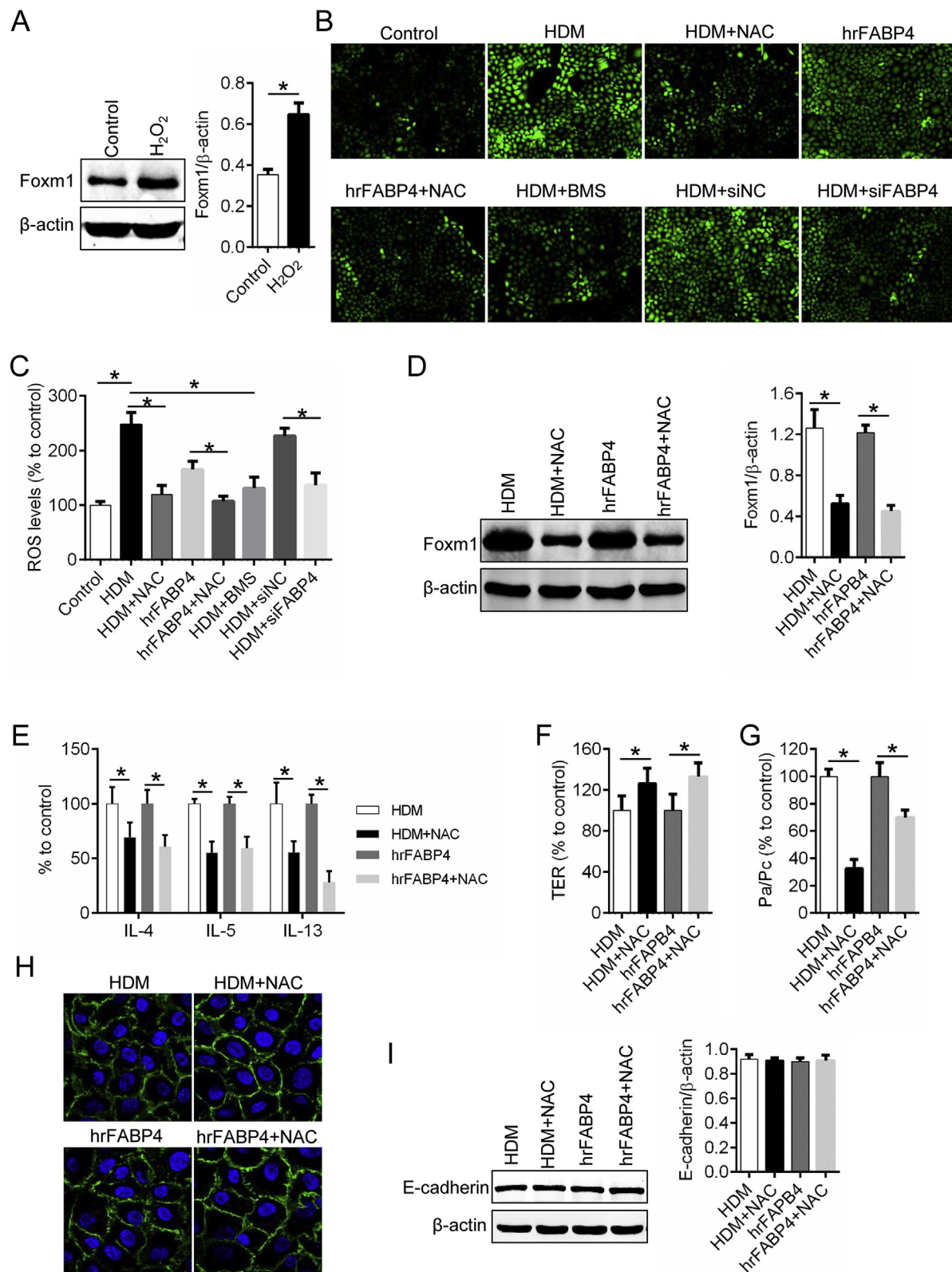


Fig. 4. HDM and hrFABP4 activated FoxM1 via ROS. (A) The expression of FoxM1 in 16-HBE was assessed by Western blot after treating by H_2O_2 . (B, C) Intracellular ROS production in 16-HBE was determined by DCF-DA fluorescence. (D) The expression of FoxM1 in 16-HBE was assessed by Western blot. (E) IL-4, IL-5, and IL-13 level in culture supernatant was determined by ELISA. Airway epithelial barrier function was valued by transepithelial electrical resistance (TER) (F) and paracellular permeability (G). The expression of E-cadherin in 16-HBE was assessed by immunofluorescence (H) and Western blot (I).

was required for allergic airway inflammation and inflammatory cell infiltration [2]. However, the relationship between FABP4 and airway barrier is still unknown. In our study, the allergic mouse exhibited increased secretion of cytokines (IL-4, IL-5, and IL-13), with disrupted epithelial barrier (lower TER, higher permeability), which could be improved by FABP4 inhibitor BMS, demonstrating that FABP4 might take part in the development of asthma. What's more, we found that the role for hrFABP4 in regulating inflammatory cytokine production and airway barrier dysfunction was similar to HDM, a classical inhaled allergen, further confirmed the role of FABP4 in allergic airway diseases.

However, how FABP4 involved in the pathological process of respiratory diseases is still unknown. Some recent reports have found that FoxM1 was also related to production of Th2 cytokines in response to HDM allergen [17,25]. Additionally, exogenous FABP4 enhanced levels of FoxM1 [18]. In our present study, it appears to have a strong correlation between FABP4 and FoxM1. HrFABP4 was shown to be responsible for upregulation of FoxM1, while siFABP4 induced a remarkably downregulation of FoxM1. This observation provided a strong indication that FABP4 take part in the pathogenesis of asthma by regulating FoxM1.

ROS have been identified as a main reason for the pathological process of asthma [26,27]. Excessive ROS production is responsible for tissue injury, airway hyper-responsiveness, and airway inflammation [4,28]. Studies have shown that inhalational allergens can promote ROS generation [29], we find that hrFABP4 can also promote ROS generation, which can be ameliorated in responsible to NAC. Besides, BMS and siFABP4 protect against HDM-induced ROS production. These data imply that FABP4 was highly relevant to ROS generation. On the other hand, H₂O₂ induced an obvious upregulation of FoxM1, which was also reported by Park's study [19]. Furthermore, NAC protect against the disruption of epithelial barrier, reduce inflammation in airway epithelial cells, and decrease the expression of FoxM1 caused by FABP4. Accordingly, we put forward the hypothesis that FABP4 may be related to the increase of FoxM1 by upregulation of ROS.

E-cadherin, an important component of tight junctions accounting for the integrity of the epithelial barrier, is regarded as the 'gatekeeper' in allergic sensitization [30,31]. HDM-induced aberrant arrangement of E-cadherin at epithelial cell-cell contact sites led to airway epithelial barrier dysfunction [30]. We found that the E-cadherin -specific fluorescence distributed around cell-to-cell was reduced after challenge with HDM and hrFABP4, yet was ameliorated contributed to pre-treatment with BMS and siFABP4. However, the expression of E-cadherin detected by Western Blotting in HDM- or hrFABP4- induced 16-HBE cells remained unchanged, while that was decreased when detected by immunofluorescence. A possible explanation for this discrepancy is that the barrier function is depending on the structural and functional abnormalities of E-cadherin but not the amount of protein expression.

In conclusion, we demonstrated that FABP4 played an important role in allergic lung disease. Upregulated ROS induced by FABP4 was of significance in activating FoxM1 leading to airway inflammation and epithelial barrier dysfunction.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.bbrc.2017.11.106>.

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4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Shaoxi Cai
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Section 1.

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xiaomin

2. Surname (Last Name)

jiang

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06-November-2017

4. Are you the corresponding author?

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☒ No

Corresponding Author's Name

Shaoxi Cai

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4. Intellectual Property.

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Section 1. Identifying Information

1. Given Name (First Name) lisha	2. Surname (Last Name) huang	3. Date 06-November-2017
4. Are you the corresponding author? ☐ Yes ☒ No		Corresponding Author's Name Shaoxi Cai
5. Manuscript Title FABP4 induces asthmatic airway epithelial barrier dysfunction via ROS-activated FoxM1		
6. Manuscript Identifying Number (if you know it) 		

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

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Section 1.

Identifying Information

1. Given Name (First Name)

shaoxi

2. Surname (Last Name)

cai

3. Date

06-November-2017

4. Are you the corresponding author?

☒ Yes ☐ No

5. Manuscript Title

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