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SLAMF7 is a key molecule that promotes M1 polarization in lung tissue macrophages of high-fat diet-fed asthma mice model

Cengceng He [1], Zhenzhen Pan [1], Yanchen Liu, Huan Zhou, Ling Li [*]

Department of Respiratory Medicine & Clinical Allergy Center, Affiliated Children's Hospital of Jiangnan University, Wuxi, 299-1 Qingyang Road, Wuxi 214023, China

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ABSTRACT

Objective: Investigating the regulatory role of Signaling lymphocyte activation molecule family 7 (SLAMF7) in the pathogenesis of asthma in a high fat-fed (HFD) mouse model, providing targets for treating obese asthma.
Methods: We constructed a mouse model of obese asthma, and Quantitative real-time RT-PCR (qPCR) for the detection of mRNA levels of SLAMF7 and M1 polarization markers of macrophages. Lung tissue levels of SLAMF7 protein, macrophage M1 polarization markers, and neutrophil markers were measured by Western blotting. The proportions of $SLAMF7^+$ macrophages and neutrophils in bronchoalveolar lavage fluid (BALF) were determined by flow cytometry. Neutrophil inflammatory cytokine levels were determined by Enzyme-linked immunosorbent assay (ELISA). Immunofluorescence performed the colocalization of SLAMF7 and inducible nitric oxide synthase (iNOS). The regulation of SLAMF7 on M1 polarization of macrophages was verified by cell experiments.
Results: The group of HFD asthmatic mice had more severe airway inflammation and mucus secretion. They also had higher SLAMF7 levels, airway neutrophil inflammation and M1 polarization of macrophages in lung tissue. SLAMF7 overexpression increased M1 polarization, and SLAMF7 knockdown decreased M1 polarization. The expression change of SLAMF7 affects the expression of NR4A1 and RUNX3, inhibiting NR4A1 and promoting RUNX3.
Conclusion: SLAMF7 expression is increased in obese asthma mice, accompanied by neutrophil infiltration and enhanced M1 polarization. SLAMF7 promotes M1 polarization may be through the NR4A1-RUNX3 axis, suppressing NR4A1, and promoting RUNX3.

1. Introduction

Asthma is a chronic inflammatory disease of the airways characterized by symptoms such as airway hyperresponsiveness, shortness of breath, chest tightness, and coughing [1]. Over 300 million people worldwide have asthma, with an incidence rate of over 10 % in many Western countries [2]. Glucocorticoids are the primary treatment for allergic asthma exacerbation. However, certain types of nonallergic asthma, such as those associated with obesity and environmental pollutants, may fail to respond to glucocorticoid therapy [3]. Obesity is a high-risk factor for asthma, and obesity asthma is a special phenotype of asthma that was first proposed by Global Strategy for Asthma in 2014 [4]. In the past, understanding asthma's pathogenesis has been limited to T helper (Th)1/Th2 imbalance. However, as research progressed, the roles of Th17 cells and innate immunity in asthma have been gradually recognized [5,6].

Unlike conventional allergic asthma, the inflammatory manifestations of obesity-related asthma are more complex. Fat tissue in obese individuals, particularly abdominal fat, secretes various pro-inflammatory factors such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, which may exacerbate chronic inflammation in the airways [7]. In addition to increasing mechanical pressure, the fat tissue in obese patients may also activate the immune system and alter the local metabolic environment, promoting the onset and worsening of asthma [8]. The symptoms of obesity-related asthma may be more persistent and harder to control, and traditional asthma treatments (such as inhaled corticosteroids and bronchodilators) may be less effective in some obese asthma patients [9].

Macrophages are a subset of innate immune cells that serve as specialized defense cells and reside within tissues. They are among the most abundant immune cells in the lungs and are crucial in asthma pathogenesis [10]. There are two forms of macrophage polarization:

* Corresponding author.
E-mail address: liling@njmu.edu.cn (L. Li).
[1] These authors contributed equally to the work.

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classically activated (M1), which is considered pro-inflammatory, and alternatively activated (M2), which is considered anti-inflammatory [11] In allergic asthma, M2 is the dominant macrophage, whereas nonallergic inflammation, M1 is the dominant macrophage [12,13]. Diet-induced obesity affects the lung immune system, which increases white blood cell counts in the lungs, and macrophages and neutrophils are polarized towards M1 and N1, respectively [14]. Moreover, Kim et al. reported that the percentage of M1 macrophages in the sputum of patients with asthma correlated with that of neutrophils [15]. These reports indicate that obesity may modify the nature of airway inflammation in allergic asthma, potentially through macrophage M1 polarization and neutrophil recruitment, leading to airway neutrophilic inflammation. However, the underlying mechanisms remain to be elucidated.

Signaling lymphocyte activation molecule family 7 (SLAMF7) primarily resides on the surfaces of cytotoxic cells, NK cells, cytotoxic T lymphocytes, mature dendritic cells, activated B cells, and monocytes. Like the other members of the SLAMF (except 2B4), SLAMF7 is a homogenous receptor that interacts with itself on neighboring cells [16,17]. Anti-CS1 mAb (elotuzumab/empliciti) has been approved by the FDA as a breakthrough drug for treating patients with Multiple Myeloma (MM). Kim, J. R. et al. reported that cross-linking SLAMF7 receptors on the cell surface reduces the production of LPS-activated human monocyte pro-inflammatory cytokines TNF-α and IL-12p70 [18]. Additionally, Choe et al. reported that the activation of SLAMF7 enhances the TLR-mediated induction of pro-inflammatory cytokines in monocytes and macrophages [19]. Marc et al. identified SLAMF7 as a novel M1-associated cell surface marker [20]. Previous studies have indicated that SLAMF7 may exert either immunostimulatory or immunosuppressive effects in various autoimmune diseases. In keratitis, SLAMF7 promotes M2 polarization through STAT6 activation, and blocking Arg-1 inhibits M2 polarization, thereby nullifying the therapeutic effect of SLAMF7 recombinant protein [21,22]. In rheumatoid arthritis and active Crohn's disease, SLAMF7 plays a central role in macrophage hyperactivation [23]. In liver cancer, SLAMF7 suppresses CCL2 signaling, enhancing M1 polarization of liver cancer macrophages [24]. In atherosclerosis, SLAMF7 also promotes foam cell formation by regulating M1 polarization [25]. However, its role in obesity-related asthma remains unclear.

A previous study found that SLAMF7 expression is significantly higher in the sputum macrophages of patients with neutrophilic asthma compared to those with non-neutrophilic asthma [26]. Hence, we hypothesized that SLAMF7 aggravates airway neutrophilic inflammation by promoting M1 macrophage polarization in obese asthma. Therefore, we established a high-fat diet (HFD)-fed asthma mouse model to investigate the effects of obesity on airway inflammation types in asthmatic mice and the role of SLAMF7 on macrophage polarization. We then confirmed our findings through cellular experiments.

2. Methods

2.1. Animal experiments

Male C57/BL6 mice (4–5 weeks old; 16 ± 2 g) were purchased from CAVENS Laboratory Animal Center (Changzhou, China). Mice were kept under a 12-h light/dark cycle and provided with water and food. All animal experiments followed the ARRIVE guidelines and the Jiangnan University Institutional Animal Care regulations. Mice were divided into four groups based on the intervention method used: lean-PBS, lean-ovalbumin (OVA), HFD-PBS, and HFD-OVA. The HFD groups received a high-fat diet containing 60 % kcal of fat (TP23300, Trophic Animal Feed High-Tech Co., Ltd, China) for 12 weeks, whereas the lean groups received a low-fat diet containing 10 % kcal of fat (TP23302, Trophic Animal Feed High-Tech Co., Ltd, China). To establish an asthma model, mice were sensitized by i.p. injection of 25 μg OVA (Sigma, United States) emulsified in 2 mg $AL(OH)_3$ gel (KX0210054, Biodragon, China) in 0.2 mL PBS (BL302A, Biosharp, China) once a week from the 12th week, three times in total. They were challenged with 3 % OVA aerosol 30 min daily for seven consecutive days starting from the 17th week using a compression atomizer (BR7553, Bairui Pharmaceutical Co., Ltd). Sham mice were sensitized and challenged with PBS as above (BL302A, Biosharp, China). Twenty-four hours after the last atomization, mice were sacrificed by intraperitoneal injection of 1 % pentobarbital for histological analysis and bronchoalveolar lavage fluid (BALF) collection. After ligating the left lung, BALF was collected from the lungs with 0.8 mL of sterile PBS in a 1-mL syringe three times. BALF cells were obtained after centrifuging the BALF at 600×*g* and 4 °C for 5 min. The study design is shown in Fig. 1C [27–30].

2.2. Histopathological examination

After collecting BALF, a portion of left lung tissue was first fixed with 4 % paraformaldehyde. The tissue was embedded in paraffin, cut into 4 μm sections, and stained with hematoxylin and eosin (H&E) [31] and Periodic Acid-Schiff (PAS) [32] to evaluate airway inflammation.

2.3. Preparation of lung single-cell suspension

Lung tissue was minced and digested in a solution containing 0.5 mg/mL Collagenase II (C8150, Solarbio, China), 0.5 mg/mL Collagenase IV(C8150, Solarbio, China), and 20 U/mL DNase I (10 mg, Sigma, Germany) at 37 °C for 1 h. Undigested fragments were filtered, centrifuged, and the supernatant discarded. The remaining tissue was resuspended in 6 mL of 40 % 1 × Percoll and layered onto 3 mL of 70 % 1 × Percoll. After centrifugation at 500*g* for 25 min, the white blood cell layer was collected, resuspended in PBS, and centrifuged again at 500*g* to isolate the leukocyte pellet.

2.4. Flow cytometry analysis

Cells from BALF and lung suspensions were prepared for flow cytometry as previously described. For surface staining, add anti-mouse Fc blocking antibody (101319, Biolegend, United States) simultaneously, cells were incubated with antibodies at 4 °C for 30 min. For intracellular staining, cells were permeabilized with fixation solution (E-CK-A109, Elabscience, China) on ice for 1 h, followed by staining for 30 min. The antibodies used include FITC anti-CD45 (157214, Biolegend, United States), PE anti-F4/80 (123109, Biolegend, United States), APC anti-Ly6G (127613, Biolegend, United States), APC anti-CD319 (152004, Biolegend, United States), PE/Cyanine7 anti-CD86 (105115, Biolegend, United States), PE/Cyanine7 anti-CD206 (141719, Biolegend, United States), and viability dye 700 (564997, Bioscience, United States). Staining was analyzed using a BD FACSAria flow cytometer and FlowJo software.

2.5. Quantitative real-time RT-PCR (qPCR) analysis

RNA was extracted from lung tissue using TRIzol reagent (Invitrogen, United States), following the manufacturer's instructions. One microgram of RNA was treated with DNase I to remove genomic DNA, and cDNA was synthesized using the HiScript III RT SuperMix Kit (R323-01, Vazyme,China). cDNA amplification was performed with ChamQ SYBR qPCR Master Mix (Q311-02/03, Vazyme, China) on a SLAN-96S PCR machine (Shanghai Hongshi Medical Technology). Transcription levels were normalized to Gapdh. Primer sequences used for qPCR are listed in Supplementary Table S1.

2.6. Western blotting (WB)

Lung tissue from three samples per group was lysed in ice-cold RIPA buffer (P0013B, Beyotime, China) with protease inhibitor. Proteins were separated by 10 % SDS-PAGE and transferred to a PVDF membrane.

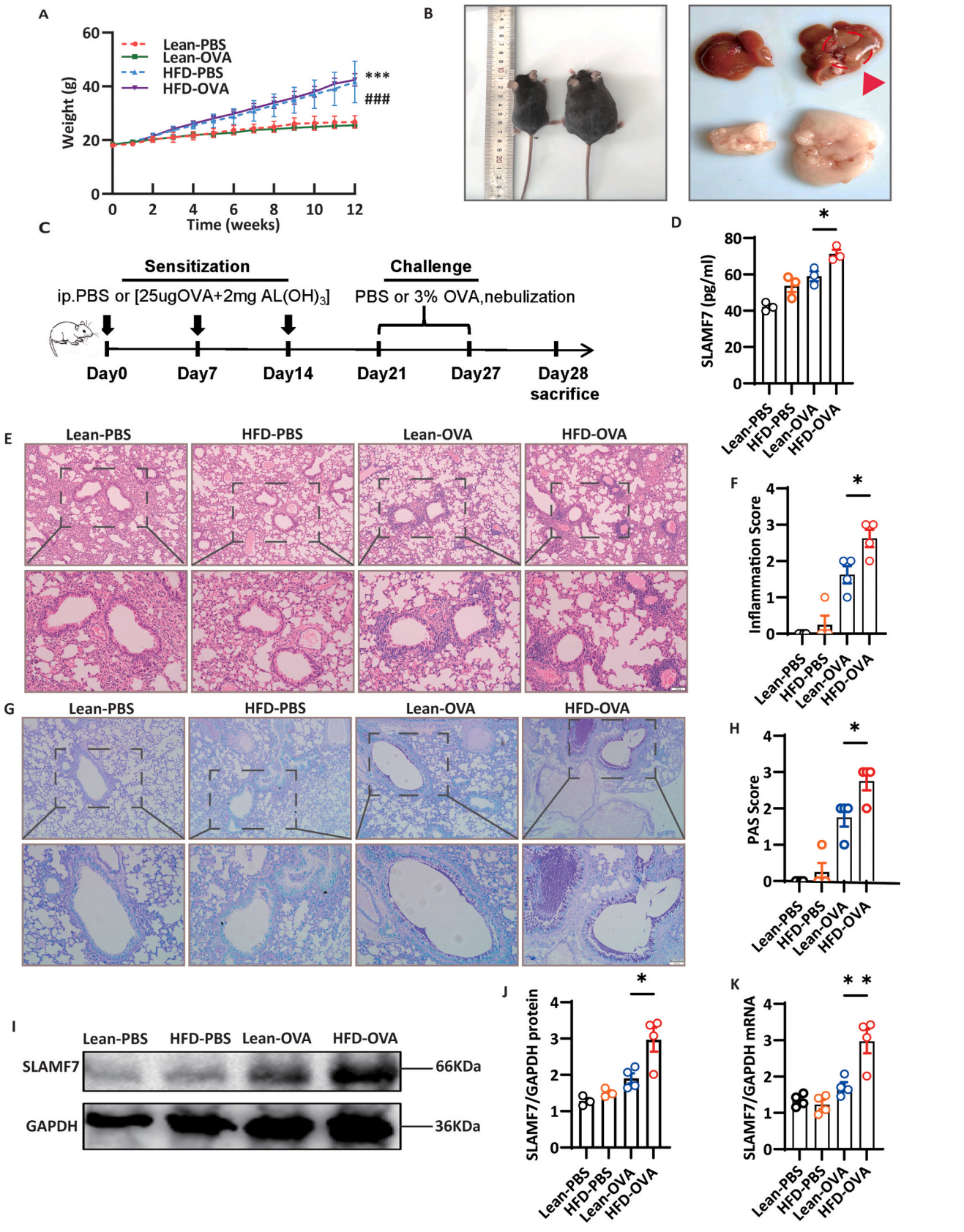

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Fig. 1. Higher SLAMF7 expression of in both lung tissue and serum from the HFD-OVA mice. (A) Trends in body weight growth in four groups of mice fed diets with varying fat content, Lean-PBS(n = 4), HFD-PBS(n = 4), Lean-OVA(n = 6), HFD-OVA(n = 6). (B) The observable changes in body weight of mice subjected to different feeding regimens. And the observable differences in the appearance of the liver and adipose tissue in mice subjected to different feeding regimens. (C) Mouse OVA sensitization model: OVA and aluminum hydroxide were used for intraperitoneal sensitization three times. One week after the last injection, 3 % OVA was used for challenge for seven consecutive days. Samples were collected after the final challenge. (D) The animal serum was analyzed using the ELISA method, with the vertical axis representing protein concentration (units: ng/mL), and the horizontal axis corresponding to different animal groups (n = 3). (E) The graph shows the mRNA expression levels of the SLAMF7 gene in lung tissues from different groups of mice. The relative expression levels of SLAMF7 in the lung tissues of each group were measured using qPCR, with the results calculated using the $2^{(-\Delta\Delta Ct)}$ method and normalized to the reference gene GAPDH. The vertical axis represents the relative mRNA expression of SLAMF7, and the horizontal axis represents the different mouse groups (n = 4). (F–G) Western blot analysis of SLAMF7 protein expression in lung tissues from different mouse groups (n = 3). (H–I) Flow cytometric analysis of the proportion of $F4/80^+$ $SLAMF7^+$ cells in BALF from different mouse groups (n = 3). (J–K) Hematoxylin and Eosin (HE) Staining of mouse lung tissue histological sections and Inflammation Score (n = 4). (L–M) PAS staining and PAS scoring of mouse lung tissue histological sections (n = 4). Histological sections showing Scale bar = 100um. **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

After blocking with 5 % nonfat milk in TBS-T, the membrane was incubated overnight at 4 °C with primary antibodies against Citrullinated Histone H3 (CitH3), inducible nitric oxide synthase (iNOS), SLAMF7, GAPDH, CD86, Ym-1, Runx3, NR4A1 and Arg-1. The membrane was then incubated with secondary antibodies for 1 h at room temperature. Protein signals were detected using an ECL kit. Primary antibody details are in Supplementary Table S2.

2.7. Cell culture and treatment

Mouse alveolar macrophages (MH-S cells) were purchased from Wuhan Sevier Biotechnology Co., Ltd. The cells were transfected for 24 h to collect RNA or for 48 h to extract protein. Lip3000 was used as the vector for plasmid or siRNA transfection. Cells were then collected for further experiments. The overexpression plasmids were purchased from abm (CS5012060). The siRNAs were purchased from GenePharma. The sequence of the overexpression plasmid is shown in Fig. 4A.

2.8. Immunofluorescence

Paraffin sections were deparaffinized with xylene and hydrated through a graded ethanol series (absolute, 90 %, 80 %, 70 %). After two washes with distilled water, antigen retrieval was performed using sodium citrate buffer. Sections were blocked with 10 % goat serum in TBST for 60 min, followed by incubation with the primary antibody at room temperature for 60 min. After washing, the secondary antibody was applied under the same conditions. Sections were mounted with antifade medium containing DAPI and observed under a fluorescence microscope within one week to prevent fluorescence quenching. Immunofluorescence was examined using an Olympus BX53 microscope. Primary antibody details are in Supplementary Table S3.

2.9. Enzyme-linked immunosorbent assay (ELISA)

The mouse eyeballs were removed to collect blood, left at room temperature for 2 h, then centrifuged at 3000 g for 20 min at 4 °C. The supernatant was collected and stored at −80 °C for the detection of SLAMF7 expression in the serum (EM2127, FineTest). The BALF supernatant was used to detect the cytokines IL-1β (EM0109-CM, FineTest), TNF-α (EM0183, FineTest), IL-6 (EM0121, FineTest), IL-8 (EM1613, FineTest), and IL-17 (EM1946, FineTest).

2.10. Isolation of human neutrophils

Human neutrophils were isolated using a neutrophil separation kit (LZS11131, TBD) following the manufacturer's instructions. For blood samples under 5 mL, 5 mL of neutrophil separation medium was added, and the sample was layered on top, centrifuged at 600*g* for 25 min. The white blood cell layer was collected, resuspended in PBS, and centrifuged again. The cells were then incubated with RBC lysis buffer on ice for 3 min, followed by PBS to stop the lysis, and centrifuged again. The neutrophil pellet was collected.

2.11. Neutrophil migration assay

Neutrophil migration was assessed using a Transwell system with a 5 μm polycarbonate membrane (3421, Corning). Conditioned medium was centrifuged to remove cells and placed in the bottom chamber. Neutrophils (2×10^5 cells/100 μL) in RPMI 1640 medium were added to the top chamber and incubated at 37 °C and 5 % CO_2 for 2 h. Migrated neutrophils were counted using the chemotactic index [33].

2.12. Neutrophil extracellular traps (NETs) detection

BALF samples were mixed with SYTOX Green dye (P11496, Thermo) as per the manufacturer's instructions and incubated at room temperature for 5 min. Fluorescence was measured using a Fluoroskan Ascent FL reader (Thermo) with the FITC channel (excitation 485 nm, emission 530 nm), and the data were analyzed accordingly.

2.13. RNA sequencing

To study gene expression changes induced by SLAMF7 overexpression in MH-S cells, total RNA was extracted from the control and SLAMF7 overexpression groups using TRIzol. High-throughput RNA sequencing was performed by Lianchuan Company. Differential gene expression was assessed by FPKM, with genes having a p-value < 0.05 considered significantly differentially expressed (DEGs).

2.14. Statistical analysis

Differences between groups were analyzed using one-way ANOVA, and statistical significance was set at $P < 0.05$. All experiments were performed in triplicate. GraphPad Prism 10 (graphpad prism 9.5.1) was used for analysis.

3. Results

3.1. Higher SLAMF7 levels of in both lung tissue and serum from the HFD-OVA mice

Compared to the lean groups, the weight of the HFD groups increased significantly ($P < 0.001$) (Fig. 1A). The HFD mice showed hepatic steatosis with an enlarged liver and increased fat volume (Fig. 1B); the Lee's Index were significantly increased ($P < 0.001$) (Supplementary Table S4 and Supplementary Fig. 1). In the HFD-OVA group of mice, a marked increase in SLAMF7 secretion was observed in the serum ($P < 0.05$) (Fig. 1D). Furthermore, in the lung tissue of HFD-OVA mice, both the mRNA ($P < 0.01$) and protein ($P < 0.05$) expression of SLAMF7 were significantly increased (Fig. 1E–G). Moreover, the proportion of $SLAMF7^+$ macrophages increased significantly in the BALF of HFD-OVA group mice (Fig. 1H, I). H&E staining showed the infiltration of inflammatory cells around the bronchi. PAS staining showed that goblet cells secreted mucus, which was associated with airway obstruction. OVA sensitization and stimulation induced significant peribronchial inflammation and goblet cell proliferation. In the mouse model, the peribronchial

inflammation and goblet cell proliferation levels were higher in HFD-OVA mice than lean-OVA mice ($P < 0.05$) (Fig. 1J–M).

3.2. Neutrophil inflammation was exacerbated in the lung tissue of HFD-OVA mice

Flow cytometry analysis revealed high neutrophil percentages in the HFD-OVA group compared to the lean-OVA group, indicating that obese asthmatic mice had higher levels of neutrophils in the BALF ($P < 0.05$) (Fig. 2A, B). Moreover, in the single-cell suspension of the lung tissue in the HFD-OVA group, the proportion of neutrophils was significantly higher than that in the other three groups ($P < 0.0001$) (Fig. 2C, D). Citrullinated Histone H3 (CitH3) expression was significantly higher in the HFD-OVA mice lung tissues than in the lean-OVA mice lung tissues ($P < 0.05$) (Fig. 2E, F). Furthermore, We measured the levels of NETs in the BALF supernatant and found a significant increase in the HFD-OVA group ($P < 0.05$) (Fig. 2G). We assessed the levels of neutrophil inflammation-related cytokines in the BALF supernatant. The results showed that in the BALF supernatant of obesity-related asthma mice, these inflammatory cytokines were all elevated ($P < 0.05$), with the neutrophil chemotactic factor IL-8 showing the most significant increase ($P < 0.01$) (Fig. 2H).

3.3. M1 polarization of macrophages in lung tissue was positively correlated with SLAMF7

The qPCR results showed that the HFD-OVA group exhibited the highest levels of M1 macrophage-related genes [iNOS ($P < 0.05$) and CD86 ($P < 0.01$)] (Fig. 3A, B). We extracted proteins from mouse lung tissue and detected the markers CD86 and iNOS for M1 macrophage polarization, Arg-1 and Ym-1 for M2 macrophage polarization. The expression levels of CD86 and iNOS proteins were significantly increased, while Arg-1 expression decreased ($P < 0.05$), and Ym-1 expression slightly decreased, but not significantly (Fig. 3C). We also detected M1 phenotype surface markers (F4/80, CD86) in the BALF to explore macrophage polarization in mouse models. The results showed that the proportion of CD86+ cells in the BALF from the HFD-OVA group was significantly increased ($P < 0.01$) (Fig. 3D, E), and the average fluorescence intensity of $CD86^{+}$ cells was highest in the HFD-OVA group ($P < 0.005$) (Fig. 3F, G). We performed semi-quantitative analysis of iNOS and SLAMF7 in lung tissue histological sections using immunofluorescence technology. The results showed that the fluorescence intensity was strongest in the HFD group, with the highest number of iNOS and SLAMF7-positive cells (Fig. 3H). Additionally, by calculating the overlap of different fluorescence signals to assess the molecular interaction, we found that SLAMF7 and iNOS were highly co-expressed in lung tissue (Fig. 3I). Flow cytometry analysis of the M1 macrophage polarization in the lung tissue and BALF showed consistent results (Supplementary Fig. 2). And we observed a significant increase in CD206 levels in the BALF of the Lean-OVA group, while the proportion of M2 macrophages in the single-cell suspension of lung tissue showed a slight increase (Supplementary Fig. 3).

3.4. SLAMF7 is a key molecule that can promote M1 polarization

To investigate how SLAMF7 expression regulates the polarization of alveolar macrophages, we used plasmids to overexpress SLAMF7 in the alveolar macrophage cell line MH-S cells and used LPS to induce M1 polarization. We compared the normal control MH-S cells with the SLAMF7-overexpressing MH-S cells by sequencing. The results showed that SLAMF7 promoted the gene expression of the M1 polarization surface markers CD86 and iNOS in MH-S cells (Fig. 4B). This result was further validated by real-time qPCR experiments, where the knockdown of SLAMF7 inhibited the expression of CD86 and iNOS (Fig. 4C, D). The expression of CD86 and iNOS proteins was significantly increased in MH-S cells, while knockdown of SLAMF7 inhibited the expression of CD86 and iNOS (Fig. 4E, F). And in culture supernatants of different grouped cells, LPS stimulated SLAMF7 MH-s cells culture supernatants significantly reduced migration relative to normal control neutrophils, whereas the culture supernatants of MH-s cells overexpressing SLAMF7 showed significantly increased migration relative to normal control neutrophils (Fig. 4G, H).

3.5. SLAMF7 promote M1 polarization by inhibiting NR4A1 expression, and promoting RUNX3 expression

We screened out genes NR4A1 and RUNX3 that may be related to M1 polarization from the differentially expressed genes identified by sequencing (Fig. 4B). Furthermore, qPCR and WB techniques were used to detect that increased expression of SLAMF7 inhibits the expression of NR4A1, but promotes the expression of the gene RUNX3; whereas knockdown of SLAMF7 promotes the expression of NR4A1 and inhibits the expression of RUNX3 (Fig. 5B, C). Subsequent western blot experiments also confirmed this at the protein level (Fig. 5A). SLAMF7 may regulate macrophage M1 polarization through the NR4A1-RUNX3 axis. We validated the expression of these two genes in the lungs of asthmatic mice fed with different diets and found that in the lung tissues of HFD-OVA mice, the mRNA expression of NR4A1 decreased, while the gene expression level of RUNX3 increased (Fig. 5E, F). The same trend was also observed at the protein level (Fig. 5D). Subsequently, we randomly tested 12 animal samples and analyzed the correlation between SLAMF7 and NR4A1, RUNX3 in their lung tissues. The results showed a strong correlation between the expression of SLAMF7 and RUNX3 ($R2 = 0.7234$, $P = 0.0005$) (Fig. 5G), but NR4A1 and SLAMF7 lacked significance (results not shown), with only a slight trend towards a negative correlation. This suggests that SLAMF7 is closely related to RUNX3 in mice and likely regulates M1 polarization through the SLAMF7-NR4A1-RUNX3 pathway.

4. Discussion

Asthma is a chronic inflammatory airway disease associated with type 2 cytokines, including interleukin-4 (IL-4), IL-5, and IL-13, which promote airway eosinophils, mucus overproduction, bronchial hyperresponsiveness, and IgE synthesis [34]. In patients with obese asthma, there is an increase in neutrophil-mediated airway inflammation [35]. Corticosteroids are currently the most cost-effective anti-inflammatory agents for treating asthma; however, patients with obese asthma often show resistance or insensitivity to them, showing poor treatment responses [36]. Corticosteroid insensitivity indicates a poorer prognosis because of limited alternative treatment options for asthma [37]. Based on differences in the type of airway inflammation caused by the immune response, asthma can be divided into type 2 and non-type 2 inflammatory asthma. In our study, we found that the proportion of neutrophils in the airways of HFD-OVA mice were significantly increased, suggesting that obesity could change the airway inflammation type in the traditional OVA-induced asthma model, leading to non-type 2 airway inflammation being dominated by neutrophils. Zhuya Yang et al. found that in obese asthma mice, the expression of neutrophil-related cytokine IL-17A, and NETs in BALF were elevated [38], which is consistent with our conclusions. In line with the findings of Yang Wang et al., our study also showed an increase in the proportion of neutrophils in the OVA-induced mouse group. Concurrently, we observed a significantdecrease in the proportion of macrophages in the BALF compared to the normal control group, with the most pronounced reduction observed in the HFD-OVA group [39]. However, in lung tissue, OVA induction led to an increase in macrophage recruitment, resulting in a significant rise in the proportion of macrophages. This may be due to the fact that alveolar macrophages, under inflammatory conditions, were more prone to oxidative stress, apoptosis, and reduced proliferation [40,41]. Regarding the results obtained from the single-cell suspension of lung tissue, we hypothesize that during inflammation, a

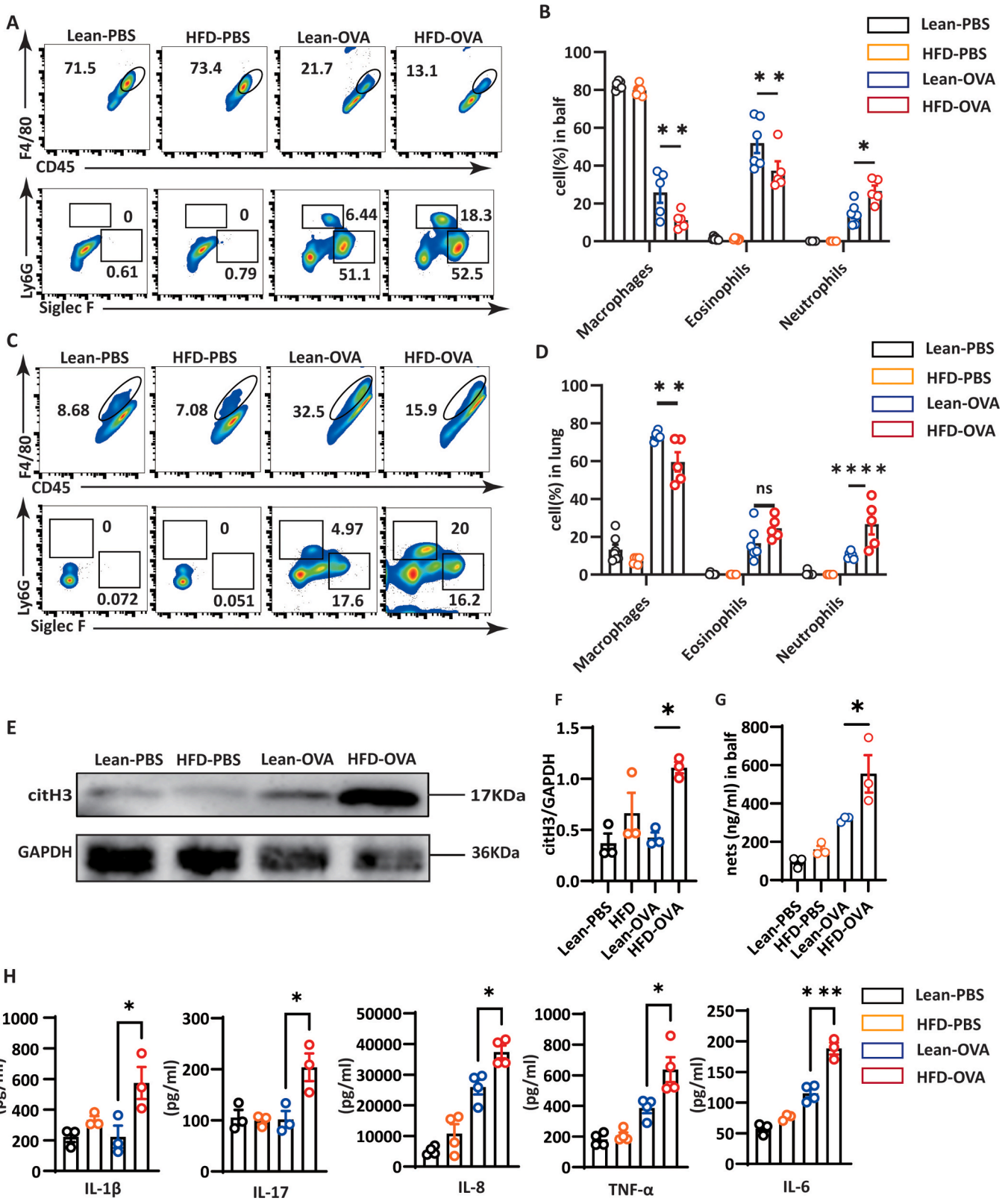

Fig. 2. Neutrophil inflammation was exacerbated in the lung tissue of HFD-OVA mice. (A–B) Flow cytometry analysis of the proportion of different leukocyte subsets in mouse BALF. Lean-PBS (n = 7), HFD-PBS (n = 6), Lean-OVA (n = 6), HFD-OVA (n = 5). (C–D) Flow cytometry analysis of the proportion of different leukocyte subsets in the lung parenchyma of mice. Lean-PBS (n = 7), HFD-PBS (n = 6), Lean-OVA (n = 6), HFD-OVA (n = 5). (E–F) Expression of citH3 protein in mouse lung tissue (n = 3). (G) Analysis of NETs content in BALF from different mouse groups and statistical analysis (n = 3). (H) ELISA analysis of neutrophil-related inflammatory cytokines in BALF supernatant from different mouse groups (n = 3 or 4). **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

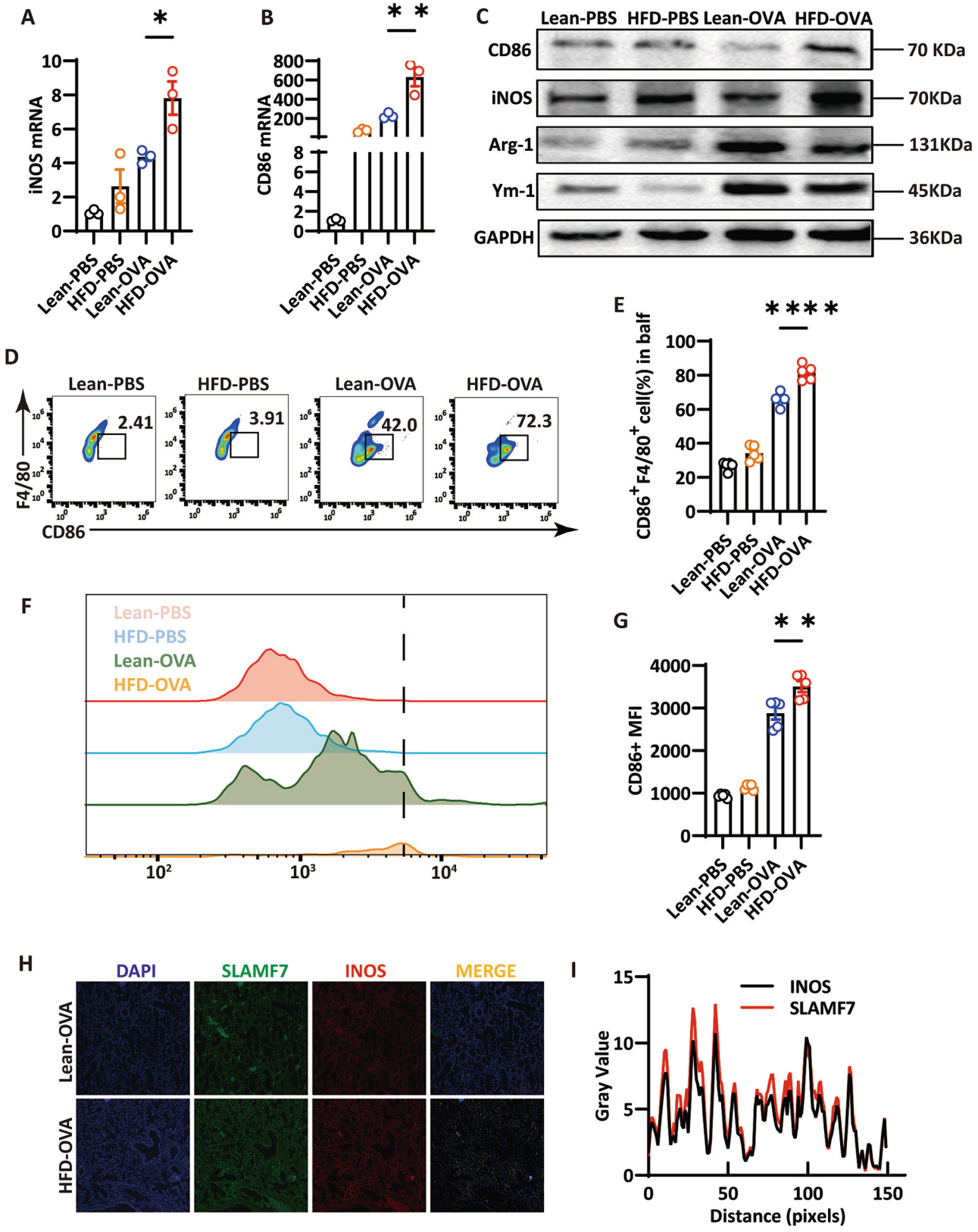

Fig. 3. M1 polarization of macrophages in lung tissure was positively correlated with SLAMF7. (A) Expression of iNOS mRNA in lung tissue (n = 3). (B) Expression of CD86 mRNA in lung tissue (n = 3). (C) Detection of CD86, iNOS, Arg-1, Ym-1, and GAPDH protein expression in lung tissue across four different groups (n = 3). (D-E) Flow cytometry analysis of the proportion of M1 macrophages ($CD86^+$ cell) in BALF across four different groups (n = 5). (F-G) Flow cytometry analysis of the MFI of M1 macrophages ($CD86^+$ cells) in BALF across four different groups (n = 5). (H-I) Immunofluorescence co-localization of iNOS and SLAMF7 in lung tissues and quantitative analysis. **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

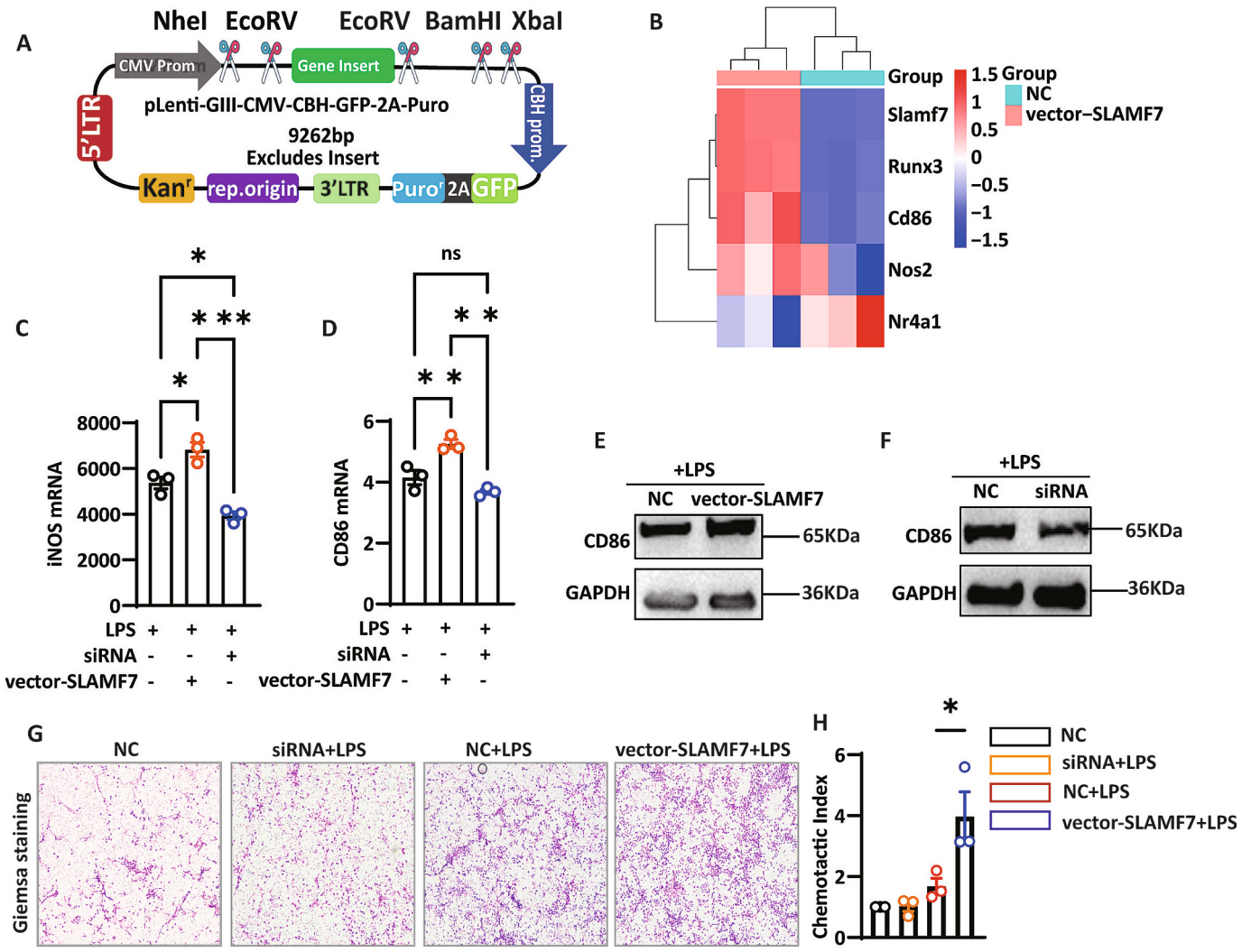

Fig. 4. SLAMF7 is a key molecule that can promote M1 polarization. (A) Structure of the SLAMF7 overexpression plasmid. (B) Differential gene expression analysis of SLAMF7-overexpressing MH-S cells vs. control cells after LPS stimulation (n = 3). (C) iNOS mRNA expression in MH-S cells under different interventions following LPS stimulation (n = 3). (D) CD86 mRNA expression in MH-S cells under different interventions following LPS stimulation (n = 3). (E–F) Western blotting was performed to analyze the expression of CD86 in mh-s cell (n = 3). (G–H) Neutrophil migration in response to supernatants from MH-S cells with different interventions during co-culture (n = 4). **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

large number of blood-derived monocytes are recruited to the airways, lung parenchyma, and perivascular regions, infiltrating the inflammatory sites, which ultimately leads to a significant increase in the proportion of macrophages in the lung parenchyma [42].

Alveolar macrophages constitute the first line of defense against inhaled air particles and microorganisms, are key to maintaining lung immune homeostasis, and are the most important immune cells [43]. A high-fat diet increases M1 macrophage infiltration into adipose tissue [44]. Asthma is not only due to Th1/Th2 imbalance, current new perspectives suggest that M1/M2 imbalance is also a causative factor for asthma. M1 cells are the major effector macrophages in nonallergic asthma, whereas M2 cells are predominant in allergic asthma [11,45]. In the lung tissue, M1 polarization of alveolar macrophages promotes neutrophil airway inflammation [29]. Jiahui Lei et al. found that the main characteristic of obesity-related asthma in obese asthma mice was non-allergic inflammation, where M1 macrophages, which primarily secrete pro-inflammatory cytokines, mediated insulin resistance and systemic metabolic inflammation in obese individuals [46]. Consistent with other studies, our research indicates an increased degree of M1 polarization of macrophages in the lung tissue of obese mouse models.

SLAMF7 is a transmembrane protein receptor with a relative molecular weight of 66 kDa, and is a member of the immunoglobulin superfamily [47]. An initial study identified SLAMF7 receptor as an activated receptor on NK cells, which regulates the cleavage function of NK cells to target cells [48]. Subsequent studies found that under normal circumstances, the SLAMF7 protein is also expressed at low levels in various human immune cells, such as partially activated T and B cell subsets, dendritic cells, mononuclear cells or macrophages, and plasma cells [21,49,50]. In recent years, the regulatory effect of SLAMF7 on macrophage function has attracted attention. Moreover, SLAMF7 has different regulatory effects on macrophage polarization in different diseases. In corneal inflammation, SLAMF7 promotes M2 polarization by inducing STAT6 activation [22]. However, in carotid atherosclerosis and hepatocellular carcinoma, SLAMF7 promotes M1 macrophage polarization [24,25]. Michael Fricker et al have performed whole genome sequencing of macrophages in induced sputum in population samples, and found that SLAMF7 was significantly elevated in samples of neutrophilic asthma patients compared to common asthma [26]. This implies that our SLAMF7 expression may be related to the recruitment of neutrophils in the airways. Interestingly, our results indicate that serum SLAMF7 levels are elevated in HFD group mice compared to Lean group mice. Moreover, in the lung tissues of obese asthmatic mice, M1

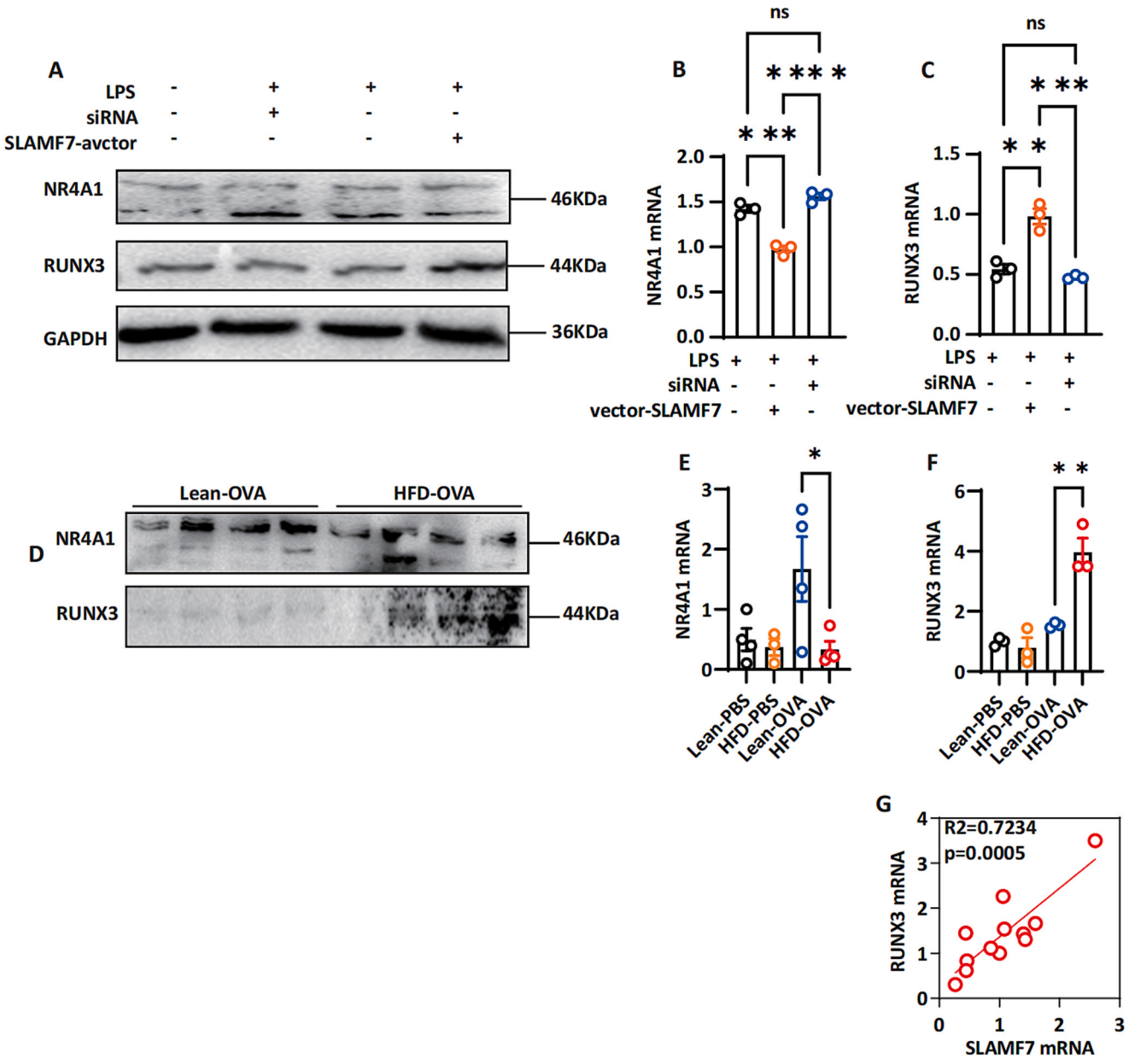

Fig. 5. SLAMF7 promote M1 polarization by inhibiting nr4a1 expression, and promoting runx3 expression. (A) Protein levels of RUNX3 and NR4A1 in MH-S cells under different interventions. (B) NR4A1 mRNA expression in MH-S cells under different interventions following LPS stimulation (n = 3). (C) RUNX3 mRNA expression in MH-S cells under different interventions following LPS stimulation (n = 3). (D) Protein levels of RUNX3 and NR4A1 in two different groups. (E) NR4A1 mRNA expression different four different groups (n = 3). (F) RUNX3 mRNA expression in different four different groups (n = 3). (G) Correlation between SLAMF7 and RUNX3 mRNA expression levels in lung tissue samples from 12 mice. **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

polarization is enhanced and the expression of M1 polarization-related inflammatory cytokines is also increased. iNOS is a surface marker protein for M1, and we performed immunofluorescence co-localization of SLAMF7 and iNOS, finding that SLAMF7 is mainly located in M1 macrophages. This suggests that SLAMF7 may affect M1 polarization. To study the association between increased SLAMF7 expression and enhanced M1 macrophage polarization, we used the mouse alveolar macrophage cell line mh-s cells, and intervened in the expression of SLAMF7 in macrophages by transfection. When SLAMF7 was overexpressed, the polarization tendency of M1 macrophages was enhanced.

We screened the NR4A1 and RUNX3 genes in the differentially expressed genes obtained by MH-s cell sequencing, which may be related to the onset of asthma [51,52]. Fengjiao Yuan et al., previously found that in atherosclerosis, SLAMF7 can promote Runx3 expression by inhibiting NR4A1 expression, and subsequently promote M1 polarization [26]. Previously, RUNX3 had focused on regulating the Th1 / Th2 balance, with RUNX3 inhibiting the development of allergic asthma and the aggregation of eosinophils, and inhibiting Th2 differentiation of helper T cells [53–55]. In our study, SLAMF7 regulated M1 / M2 polarization in the lung tissue of asthmatic mice by regulating the NR4A1-RUNX3 axis, promoting M1 polarization and recruited more neutrophils and prompting the development of non-allergic airway inflammation. This study only observed altered SLAMF7 expression in animals, and through a series of experiments guessing its possible modulation of M1 polarization and neutrophil recruitment, followed by intervention experiments using in vitro cell lines, but no intervention for SLAMF7 gene expression in animals, and the results have certain limitations.

5. Conclusion

Our study demonstrated that SLAMF7 expression is increased in obese asthma mice, accompanied by neutrophil infiltration and enhanced M1 polarization. SLAMF7 promotes M1 polarization may be through the NR4A1-RUNX3 axis. Further in vivo mechanistic studies are needed to elucidate the specific mechanisms.

CRediT authorship contribution statement

Cengceng He: Writing – original draft, Visualization, Resources, Data curation. **Zhenzhen Pan:** Writing – review & editing, Methodology, Conceptualization. **Yanchen Liu:** Software, Formal analysis. **Huan Zhou:** Investigation. **Ling Li:** Validation, Supervision, Project administration.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2025.114203.

Data availability

Data will be made available on request.

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Glossary

BALF: bronchoalveolar lavage fluid
H&E: hematoxylin and eosin
HFD: high-fat diet
IL: interleukin
M1: classically activated
M2: alternatively activated
NET: neutrophil extracellular trap
OVA: ovalbumin
PAS: periodic acid-Schiff
SLAMF7: signaling lymphocyte activation molecule family 7
Th: T helper
TNF: tumor necrosis factor.