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ORIGINAL RESEARCH

Oncostatin M Drives Th2 Polarized Allergic Airway Inflammation Through Fibroblast Reprogramming and Endoplasmic Reticulum Stress

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Background: Allergic airway inflammation, characterized by Th2 cytokine production and eosinophilic infiltration, is a hallmark of asthma. The airway epithelium plays a pivotal role in orchestrating allergic responses by releasing cytokines such as oncostatin M (OSM). This study investigates the role of OSM in dust mite extract (DME)-induced allergic airway inflammation and identifies a novel mechanism by which OSM drives Th2-polarized inflammation.

Methods: A murine model of DME-induced airway inflammation was established. Mice were treated with CelEd, a nanoparticle carrying fibroblast-targeting device and ATF4 siRNA.

Results: We observed that DME exposure significantly upregulates OSM expression in airway epithelial cells, both at the mRNA and protein levels. This finding was corroborated in human bronchial epithelial cell lines, where DME exposure induced dose-dependent OSM secretion. Intranasal administration of OSM in naïve mice phenocopied the hallmark features of allergic inflammation, including eosinophilic infiltration and elevated Th2 cytokines, highlighting OSM's sufficiency to drive allergic responses. Mechanistically, we discovered that OSM promotes IL-4 production through fibroblast reprogramming, involving endoplasmic reticulum stress (ERS) activation. OSM signaling in fibroblasts led to ERS and subsequent activation of the PERK-eIF2α-ATF4 pathway, which drives IL-4 transcription via the ATF4/Mef2d/GATA3 axis. Importantly, targeting this pathway through fibroblast-specific ATF4 knockdown significantly alleviated allergic pathology, including airway eosinophilia, Th2 cytokine production, and airway hyperresponsiveness.

Conclusion: These findings underscore the critical role of OSM in allergic airway inflammation and identify the OSM-ERS-IL-4 axis as a potential therapeutic target for asthma and other allergic diseases.

Keywords: Oncostatin M, OSM, endoplasmic reticulum stress, ERS, IL-4, airway fibroblasts, allergic airway inflammation

Introduction

Allergic airway inflammation is a central pathological feature of asthma, characterized by the activation of Th2 immune responses, eosinophilic infiltration, and airway remodeling.[1–3] Despite significant advances in understanding the pathogenesis of asthma, the mechanisms underlying the initiation and perpetuation of Th2-polarized inflammation remain incompletely understood.[4–6] The airway epithelium, traditionally viewed as a passive barrier, has now emerged as a key orchestrator of allergic responses.[7–9] Upon allergen exposure, airway epithelial cells become activated and release a variety of cytokines and chemokines that shape the immune microenvironment, thereby driving allergic inflammation.[7,10,11]

Among the cytokines expressed by airway epithelial cells, oncostatin M (OSM) has garnered increasing attention as a critical mediator in allergic diseases.[12] OSM, a member of the interleukin-6 (IL-6) cytokine family, is known for its

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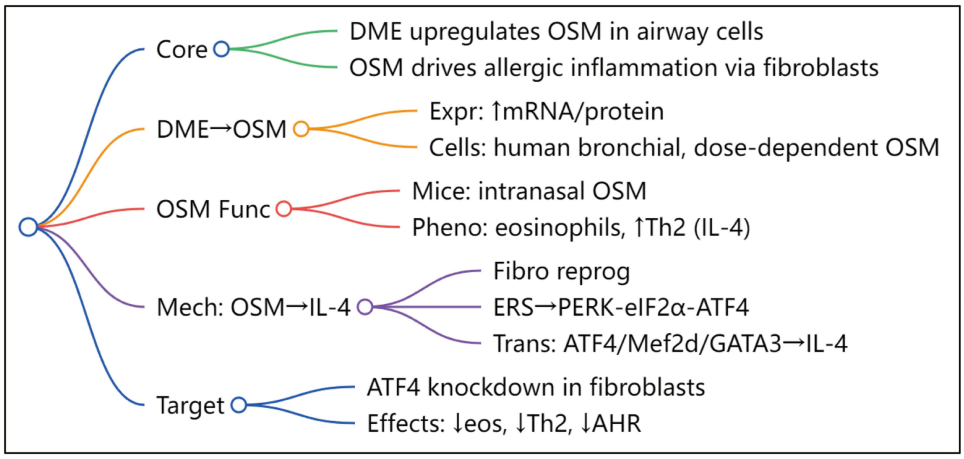
Graphical Abstract



diverse roles in inflammation, immunity, and tissue repair.[13] Recent studies have implicated OSM in driving airway remodeling and hyperresponsiveness in experimental asthma models, suggesting its potential as a therapeutic target.[7,10] However, the specific role of OSM in allergic airway inflammation, particularly its expression and function in airway epithelial cells, remains poorly understood.

In this study, we investigated the role of OSM in dust mite extract (DME)-induced allergic airway inflammation. We demonstrated that DME exposure triggers significant upregulation of OSM expression in airway epithelial cells, both in murine models and human bronchial epithelial cell lines. Furthermore, we identified a novel mechanism by which OSM promotes Th2-polarized inflammation through fibroblast reprogramming and endoplasmic reticulum stress (ERS) activation. Specifically, OSM signaling in fibroblasts induces ERS and subsequent activation of the PERK-eIF2α-ATF4 pathway, which drives IL-4 transcription via the ATF4/Mef2d/GATA3 axis. Importantly, targeting this pathway through fibroblast-specific ATF4 knockdown significantly alleviated allergic pathology, highlighting its potential as a therapeutic strategy for asthma.

Our findings provide novel insights into the role of OSM and its downstream pathways in allergic airway inflammation. By identifying the airway epithelium as a primary source of OSM during allergic challenge and uncovering the molecular mechanisms linking OSM to Th2 cytokine production, this study advances our understanding of the pathogenesis of allergic diseases. Furthermore, the identification of the ATF4/Mef2d/GATA3 axis as a key driver of IL-4 transcription opens new avenues for therapeutic intervention in asthma and other allergic diseases.

Materials and Methods

Dust Mite Extract (DME)-Induced OSM Expression in Airway Epithelium

Animal Model

- DME-induced inflammation: BALB/c mice (6–8 weeks old, male/female, n=6/group) received daily intranasal instillation of DME (50 μg in 50 μL PBS) or PBS control for 14 days.
- Sample collection: $CD45^{-}EpCAM^{+}$ airway epithelial cells were isolated by flow cytometry (FACSAria III, BD Biosciences). BALF was collected via tracheal lavage with 0.5 mL PBS.
- Ethics approval: Experiments were approved by the Shenzhen University Animal Ethics Committee (No. A202401380) and conducted in accordance with the ARRIVE guidelines and GB/T 35892–2018 (China).

Cell Culture

- Human bronchial epithelial cells: 16HBE and BEAS-2B cells were cultured in DMEM/F12 (Gibco) with 10% FBS at 37°C/5% CO_2, then treated with DME (0–100 μg/mL) for 48 hours. Cells and supernatants were harvested for downstream analysis.

Analytical Methods

- qRT-PCR: Total RNA was extracted using TRIzol (Invitrogen), reverse-transcribed with SuperScript III (Invitrogen), and quantified by SYBR Green PCR (Roche) on a CFX96 Real-Time System (Bio-Rad). Primers are listed in Table S1.
- ELISA: OSM protein in BALF and cell supernatants was measured using a commercial kit (R&D Systems, DY295) per manufacturer's instructions.

Epithelial-Derived OSM Drives Th2 Inflammation

OSM Administration Model

- Intranasal delivery: Naïve mice received daily intranasal OSM (50 μg/kg in PBS) or vehicle control for 7 days.

BALF Analysis

- Cellular profiling: BALF pellets were resuspended in PBS, and total cells were counted via Trypan Blue exclusion. Eosinophils were quantified by Diff-Quik staining (Sigma-Aldrich) and morphological identification.
- Cytokine quantification: IL-4, IL-5, and IL-13 in BALF were measured using a Luminex Multiplex Assay (Millipore, MCYTOMAG-70K) on a MAGPIX system (Luminex).

OSM Induces IL-4 Production via Fibroblast Reprogramming

In vitro Studies

- Fibroblast treatment: WI-38 and MRC-5 cells (ATCC) were stimulated with OSM (10–100 nM) for 48 hours or transfected with OSMR siRNA (Santa Cruz, sc-137176) using Lipofectamine 3000 (Invitrogen).

Knockdown validation: OSMR mRNA levels were assessed by qPCR, confirming ≥75% knockdown efficiency.

In vivo Validation

- Fibroblast-specific OSMR KO mice: *Col1a2*-Cre × *Osmr*$^{fl/fl}$ mice (Jackson Laboratory) were generated and treated with intranasal OSM for 7 days.
- Tissue analysis: Lung fibroblasts were isolated by laser microdissection (Leica LMD7000). IL-4 mRNA (qPCR) and protein (ELISA, R&D Systems DY204) were quantified in cell lysates/homogenates.

Endoplasmic Reticulum Stress (ERS) Mediates OSM-IL-4 Signaling

Transcriptomic Profiling

- RNA sequencing: Total RNA from lung fibroblasts (n=6/group) was sequenced on an Illumina NovaSeq 6000 (PE150). DEGs were identified using DESeq2 ($|\log2FC|>1$, $p<0.05$), followed by GO/KEGG enrichment via DAVID 2021.

Protein Detection

- Pharmacological inhibition: Fibroblasts were pretreated with GSK2606414 (0.4 nM, PERK inhibitor; Selleckchem, S7364) for 1 hour before OSM stimulation.

ATF4/Mef2d/GATA3 Synergistically Activates IL-4 Transcription

Molecular Interaction Studies

- Co-immunoprecipitation (Co-IP): Lung fibroblast lysates from OSM-treated mice were immunoprecipitated with ATF4 antibody (Santa Cruz, sc-390451) and Protein A/G beads, followed by WB analysis for Mef2d (Cell Signaling, 5372).

Molecular docking: ATF4-Mef2d interactions were predicted using SwissDock and visualized with PyMOL.

Luciferase Reporter Assay

- Vector construction: The IL-4 promoter (−2000 to +200 bp) was cloned into pGL4.10 (Promega). HEK293 cells were co-transfected with ATF4, Mef2d, or GATA3 plasmids (Origene) using Lipofectamine 2000.
- Dual-luciferase assay: Activity was measured 48 hours post-transfection (Promega Dual-Luciferase Kit) on a GloMax Discover System (Promega).

In vivo Intervention

- ATF4 inhibition: Mice received ATF4-IN-2 (10 mg/kg, i.p.; Selleckchem, S8237) with OSM for 7 days. Mef2d/GATA3 binding to the IL-4 promoter was assessed by ChIP-qPCR (Antibodies: Mef2d, Abcam ab19802; GATA3, Santa Cruz sc-25310).

ATF4-Targeted Therapy in Allergic Asthma

Nanoparticle Preparation

See Supplementary Materials and Figures S1–S3 for detailed protocols.

Asthma Model and Treatment

- Dust mite extract (DME) sensitization/challenge: Mice were i.p. injected with DME (100 μg) + alum on days 0/7, followed by intranasal DME (50 μg) on days 14–28.
- Therapeutic regimen: ATF4 siRNA nanoparticles (2 mg/kg) were administered via tail vein injection (3×/week for 2 weeks).

Endpoint Evaluation

- Airway hyperresponsiveness (AHR): Penh values were measured via whole-body plethysmography (Buxco) after methacholine challenge (6.25–50 mg/mL).
- Histopathology: Lungs were fixed in 4% PFA, paraffin-embedded, sectioned, and stained with H&E for inflammation scoring by blinded reviewers.

Statistical Analysis

- Data are presented as mean ± SD ($n \geq 3$ independent experiments).
- Comparisons: Student's *t*-test (two groups) or ANOVA with Tukey's post hoc test (multiple groups).
- Correlations: Pearson or Spearman tests (depending on data distribution).
- Significance thresholds: $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$.

Results

DME Exposure Induces Epithelial OSM Expression in Allergic Airways

To characterize epithelial responses to allergens, we established a murine model of DME-induced airway inflammation via 14 days of intranasal DME instillation. Flow-sorted $CD45^{-}EpCAM^{+}$ airway epithelial cells showed a 10.85-fold increase in OSM mRNA ($p<0.01$) and 5.34-fold elevation in BALF OSM protein ($p<0.0001$) compared to PBS controls (Figure 1A and B). In human bronchial epithelial cells (16HBE and BEAS-2B), DME exposure (0–100 μg/mL for 48 h) induced dose-dependent OSM secretion, confirming the airway epithelium as a primary OSM source during allergic challenge (Figure 1C and D).

Epithelial-Derived OSM Orchestrates Th2-Polarized Inflammation

DME-challenged mice exhibited hallmark Th2 inflammation:

1. 4.3-fold increase in BALF eosinophil counts ($p<0.0001$);
2. Elevated Th2 cytokines (IL-4: 2.76-fold, IL-5: 5.77-fold, IL-13: 7.91-fold vs controls) and phosphorylated GATA3/STAT6 in lung $CD4^{+}$ T cells (Figure 2A–F);

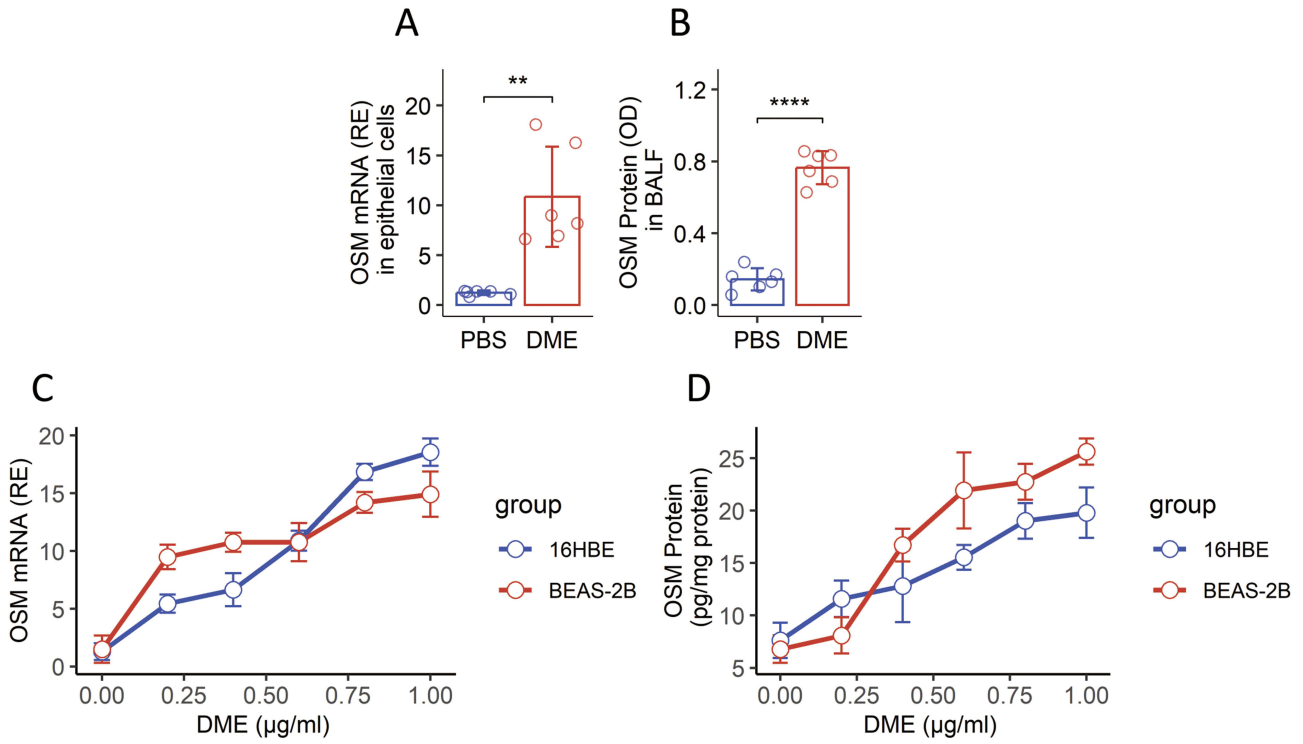


Figure 1 Dust mite extract (DME) induces oncostatin M (OSM) expression in airway epithelial cells. (**A** and **B**) Mice received daily intranasal DME instillation for 2 weeks. Airway epithelial cells and bronchoalveolar lavage fluid (BALF) were collected for analysis. Bar graphs show OSM mRNA levels in epithelial cells (**A**) and OSM protein concentrations in BALF (**B**). (**C** and **D**) Human bronchial epithelial cell lines (16HBE and BEAS-2B) were treated with DME for 48 hr. Line graphs display OSM mRNA expression (**C**) and secreted OSM protein in culture supernatants (**D**). Individual data points (dots) and mean ± SD are shown. Statistical analysis: Student's *t*-test; **$p<0.01$; ****$p<0.0001$. RE: Relative expression. OD: Optical density.

3. Strong correlations between epithelial OSM mRNA and BALF eosinophilia (r=0.85) or Th2 cytokines (r=0.62–0.79, p<0.05–0.001) (Figure 2G).

   Intranasal OSM administration (50 μg/kg for 7 days) in naïve mice recapitulated these phenotypes, demonstrating OSM sufficiency to drive allergic inflammation (Figure 2H–M).

OSM Induces IL-4 Production via Fibroblast Reprogramming

Recombinant OSM (10–100 nM) induced dose-dependent IL-4 expression in human lung fibroblasts (WI-38: EC_{50}=28.4 nM; MRC-5: EC_{50}=41.7 nM) (Figure 3A and B). OSMR knockdown (75% efficiency, Figure 3C) abolished IL-4 induction (p<0.001, Figure 3D and E). In vivo, OSM-treated mice showed 2.52-fold higher fibroblast IL-4 mRNA (p<0.01) and 2.01-fold increased lung IL-4 protein, effects abrogated in fibroblast-specific $OSMR^{-/-}$ mice (Figure 3F and G).

ERS Activation Mediates OSM-IL-4 Signaling

Transcriptomic analysis revealed OSM-induced endoplasmic reticulum stress (ERS) in fibroblasts, marked by:

1. Upregulation of ERS mediators (Perk: 6.2-fold, Eif2a: 5.8-fold, Atf4: 4.5-fold);
2. Concurrent Th2 gene activation (Gata3: 3.1-fold, Il4: 4.8-fold) (Figure 4A–D);
3. Phosphorylation cascades (p-PERK: 6.8-fold, p-eIF2α: 6.5-fold, p<0.01) and nuclear ATF4 translocation (4.8-fold, p<0.01) (Figure 4E–H).

   PERK inhibition (GSK2606414, 1 μM) reduced OSM-induced IL-4 by 73% (p<0.001, Figure 4H). IL-4 strongly correlated with ERS markers (r=0.65–0.88) and BALF Th2 parameters (r=0.71–0.81, p<0.05–0.001) (Figure 4I).

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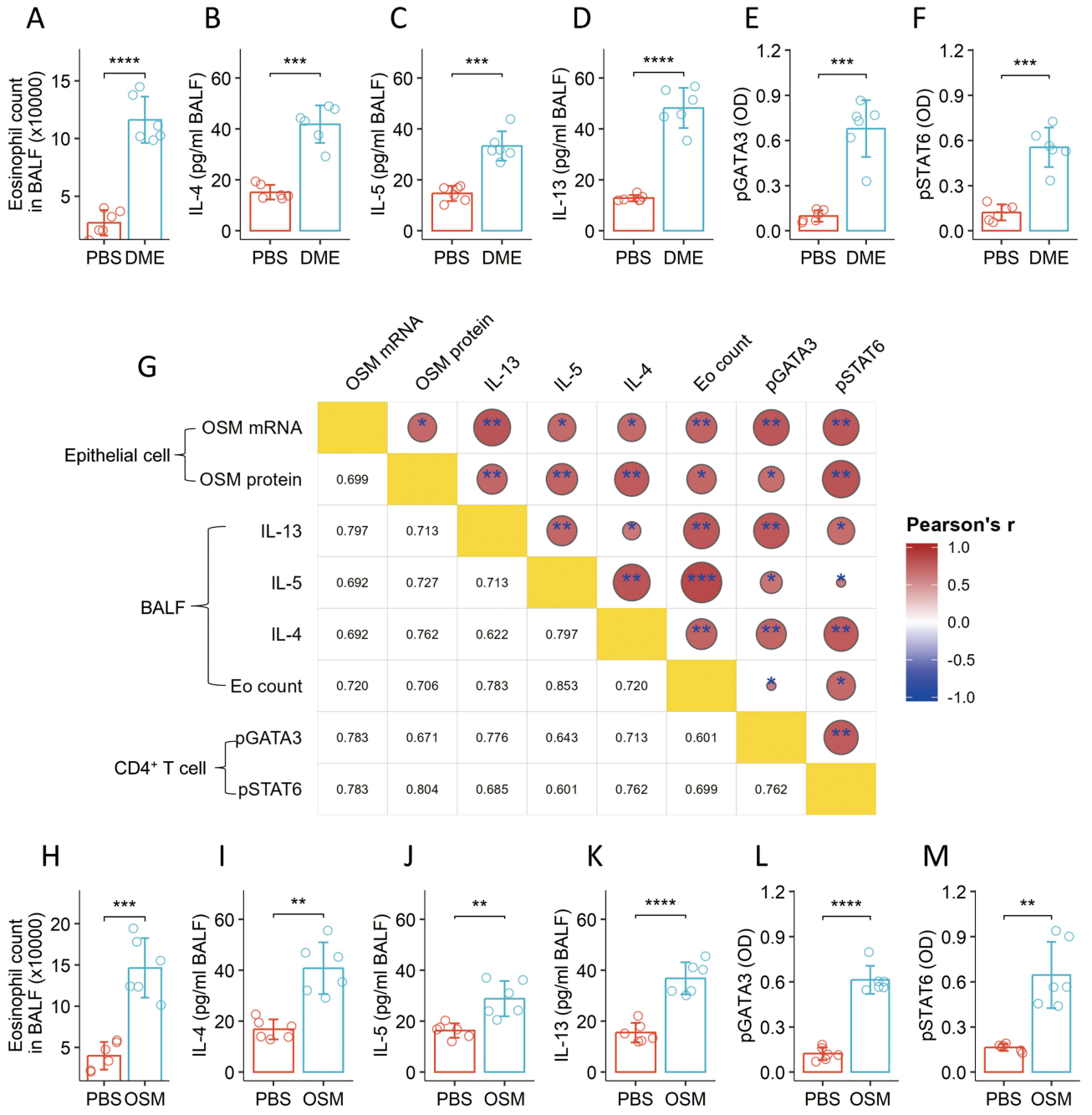

Figure 2 Airway epithelial-derived oncostatin M (OSM) drives Th2-polarized airway inflammation. (**A-G**) Mice underwent nasal instillation of OSM to assess inflammatory responses. (**A**) Eosinophil counts in bronchoalveolar lavage fluid (BALF) by flow cytometry. (**B-D**) Levels of Th2 cytokines (IL-4, IL-5, IL-13) in BALF. (**E-F**) Phosphorylated GATA3 (pGATA3) and phosphorylated STAT6 (pSTAT6) expression in lung-isolated $CD4^+$ T cells, measured by flow cytometry. (**G**) Pearson correlation analysis between epithelial OSM expression (from Figure 1) and BALF parameters (eosinophil counts, Th2 cytokines) as well as pGATA3/pSTAT6 levels in $CD4^+$ T cells. (**H-M**) Naïve mice received daily OSM treatment (50 μg/kg, i.n.) for 7 days: (**H**) Eosinophil infiltration in lung tissue sections (quantified by histology). (**I-K**) Th2 cytokine levels (IL-4, IL-5, IL-13) in BALF. (**L-M**) pGATA3 and pSTAT6 expression in lung-isolated $CD4^+$ T cells. Data are presented as mean ± standard deviation (SD), with individual data points overlaid. Statistical analyses: Student's *t*-test for (A-D, H-M); Pearson correlation for (G). Significance levels: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. OD: Optical density.

ATF4/Mef2d/GATA3 Synergy Drives IL-4 Transcription

Co-immunoprecipitation confirmed pPERK (Figure 5A) and ATF4-Mef2d complex formation in OSM-treated fibroblasts (Figure 5B and C). Structural modeling identified key binding residues (ATF4: GLU/ASP; Mef2d: VAL/GLU) (Figure 5D). ATF4 co-expression enhanced nuclear Mef2d translocation (Figure 5E and F), while ATF4 inhibition reduced Mef2d binding to the Gata3 promoter and GATA3 recruitment to the Il4 promoter (Figure 5G and H). Luciferase

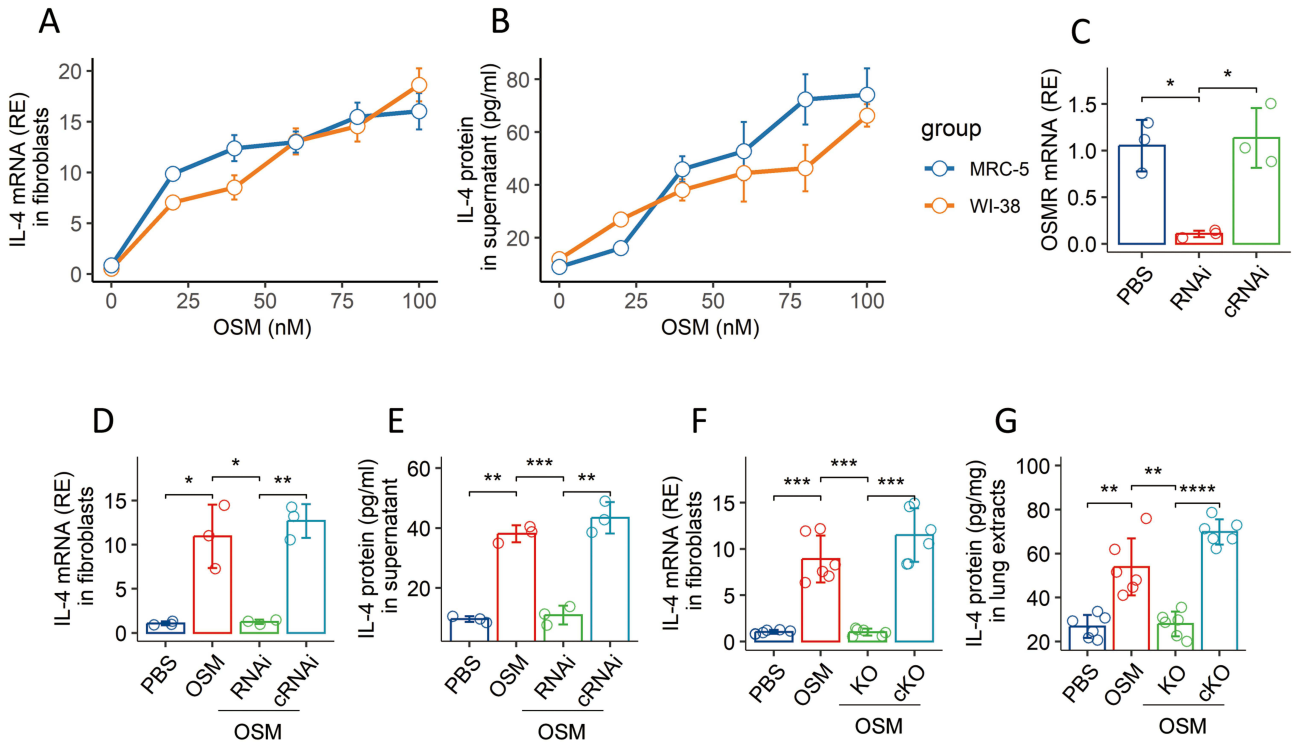

Figure 3 OSM promotes IL-4 production in airway fibroblasts. (**A-B**) IL-4 expression profiles in fibroblast lines following 48 hr OSM exposure. (**C**) OSMR knockdown efficiency in WI-38 cells. (**D-E**) IL-4 mRNA (**D**) and protein (**E**) levels after OSMR RNAi. (**F-G**) In vivo OSM administration (7 days): IL-4 mRNA in lung fibroblasts (**F**) and protein in lung homogenates (G). Data shown as mean ± SD with individual points. Statistical analysis: ANOVA with Tukey's test; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. RE: Relative expression.

assays showed 14.09-fold IL4 promoter activation requiring ATF4/Mef2d/GATA3 co-expression (Figure 5I), with corresponding IL-4 upregulation in fibroblasts (Figure 5J and K).

ATF4 Targeting Alleviates Allergic Pathology

In DME-sensitized mice, fibroblast-targeted ATF4 siRNA nanoparticles (82.45% knockdown efficiency; Supplementary Material and Figures S1-S3) significantly attenuated:

1. Airway eosinophilia (59% reduction, p<0.01) (Figure 6A);
2. Th2 cytokines (IL-4: 61.2%, IL-5: 64.3%, IL-13: 60.5% reduction, p<0.001) (Figure 6B–D);
3. Histopathological damage (Figure 6E);
4. Methacholine-induced AHR (42% lower Penh at 25 mg/mL, p<0.05) (Figure 6F).

Discussion

Allergic airway inflammation, a cardinal feature of asthma, is defined by Th2 cytokine dominance, eosinophilic infiltration, and airway hyperresponsiveness.[14,15] While the airway epithelium is recognized as a key initiator of allergic responses, the molecular pathways linking epithelial activation to downstream inflammatory cascades remain incompletely characterized.[16,17] This study identifies oncostatin M (OSM) as a central mediator bridging epithelial stress responses to Th2 polarization, via fibroblast reprogramming and endoplasmic reticulum stress (ERS) activation. Our data show that airway epithelial cells rapidly upregulate OSM in response to dust mite extract (DME), and that OSM alone is sufficient to orchestrate Th2-polarized inflammation. Mechanistically, we uncover a novel OSM-ERS-ATF4/Mef2d/GATA3 axis driving IL-4 production, highlighting therapeutic opportunities for allergic disease intervention.

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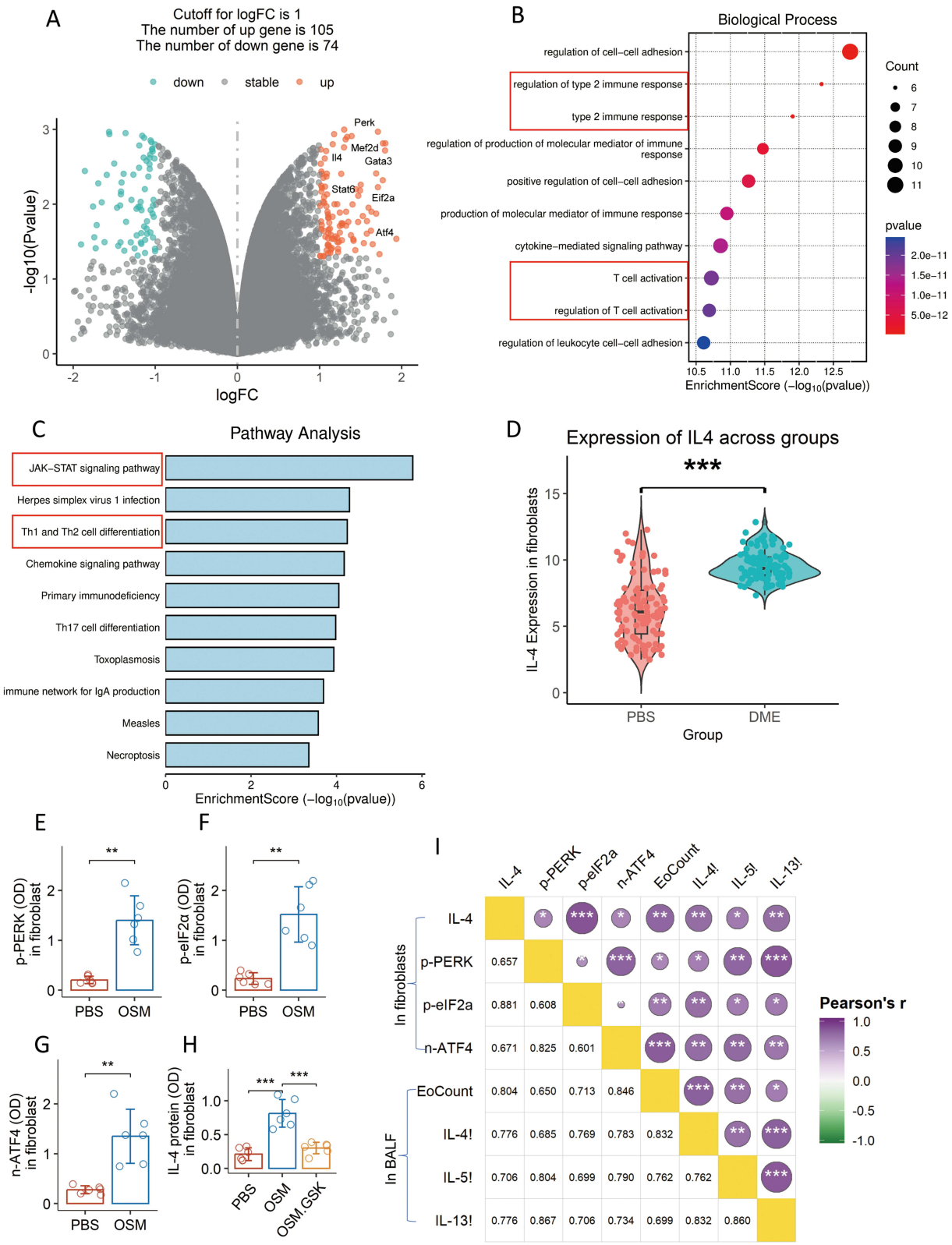

Figure 4 Transcriptomic profiling of OSM-activated airway fibroblasts. Lung fibroblasts from OSM- or PBS-treated mice (n=6/group) underwent RNA sequencing. (**A**) Volcano plot of differentially expressed genes (DEGs). (**B-C**) Th2-associated biological processes (**B**) and enriched pathways (C, red boxes). (**D**) Violin plot of Il4 expression. (**E-H**) Protein levels of endoplasmic reticulum stress (ERS) markers and IL-4. (**I**) Correlation heatmap between fibroblast parameters and BALF components. Data presented as mean ± SD (**D** and **E**) with individual points. Statistics: Student's *t*-test (**D** and **E**) and Pearson's correlation (F). **p*<0.05. ***p*<0.01; ****p*<0.001. Raw data (A-D): BioProject PRJNA1111232; SRA SRP508146. Abbreviations: IL-4/IL-5/IL-13 (samples from OSM-treated mice); p-PERK/p-eIF2α (phosphorylated forms); n-ATF4 (nuclear translocated); GSK (PERK inhibitor GSK2606414, 0.4 nM).

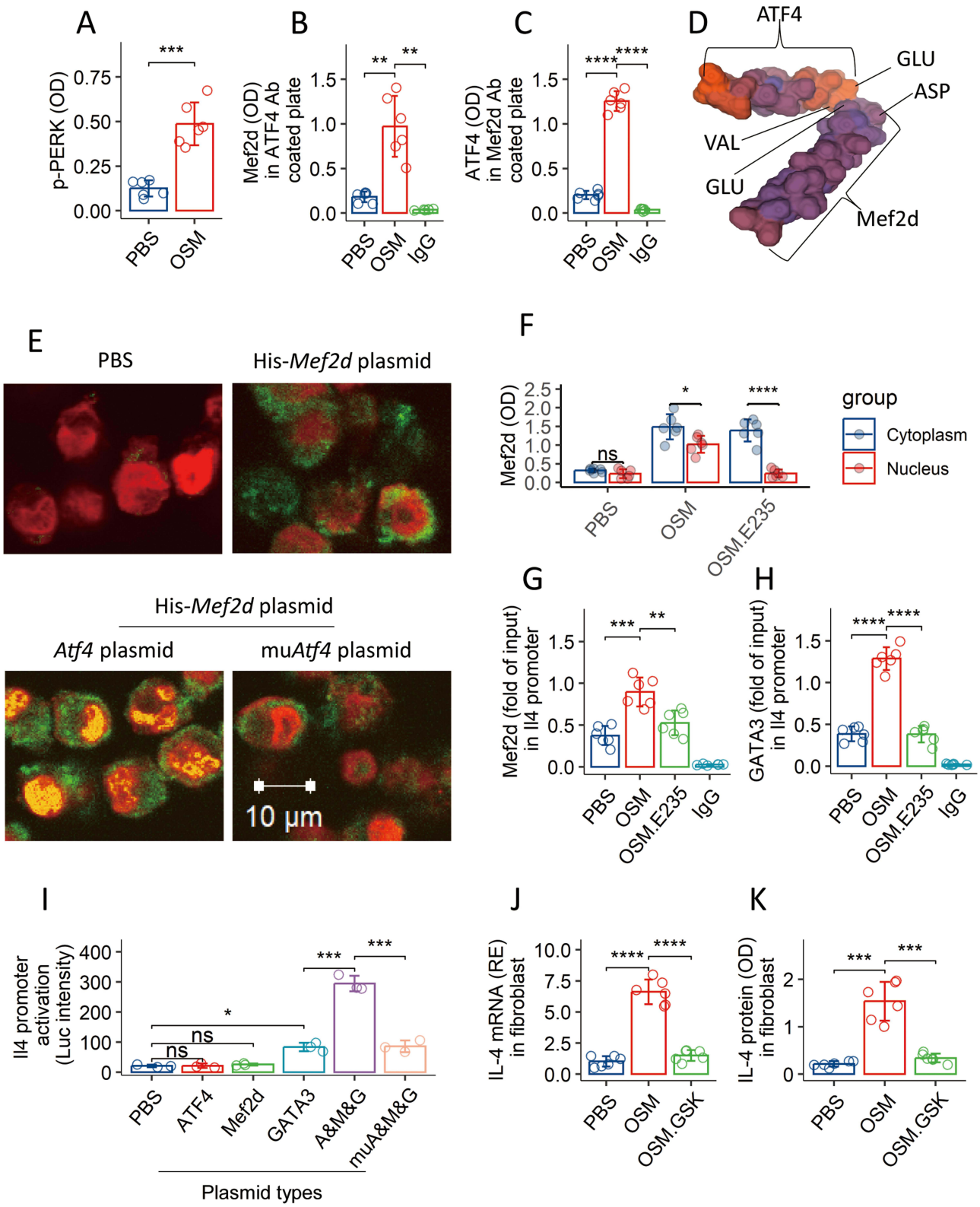

Figure 5 Synergistic activation of IL-4 promoter by ATF4-Mef2d-GATA3 axis.A, the amount of phosphorylated PERK (pPERK) in lung fibroblasts. (**B** and **C**) Immunoprecipitation showing ATF4-Mef2d interaction in lung fibroblasts from OSM-treated mice. (**D**) Predicted ATF4-Mef2d complex structure. (**E**) Confocal microscopy (630×) of subcellular His-Mef2d localization (in green) in ATF4-transfected HEK293 cells (the nuclei were stained with propidium iodide in red). (**F–H**) Cytoplasm Mef2d (F), nuclear Mef2d (**G**) and GATA3 (**H**) levels. E235 (5 μM; MCE): An inhibitor of ATF4. (**I**) Luciferase reporter assay of IL-4 promoter activation (A: ATF4; (**M**) Mef2d; (**G**) GATA3; muA: ATF4 mutant). (**J–K**) IL-4 mRNA (**I**) and protein (**J**) levels. GSK: (GSK2606414; 0.4 nM; MCE): An inhibitor of PERK. Data shown as mean ± SD with individual points. Statistical analysis: ANOVA with Tukey's test; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. OD: Optical density.

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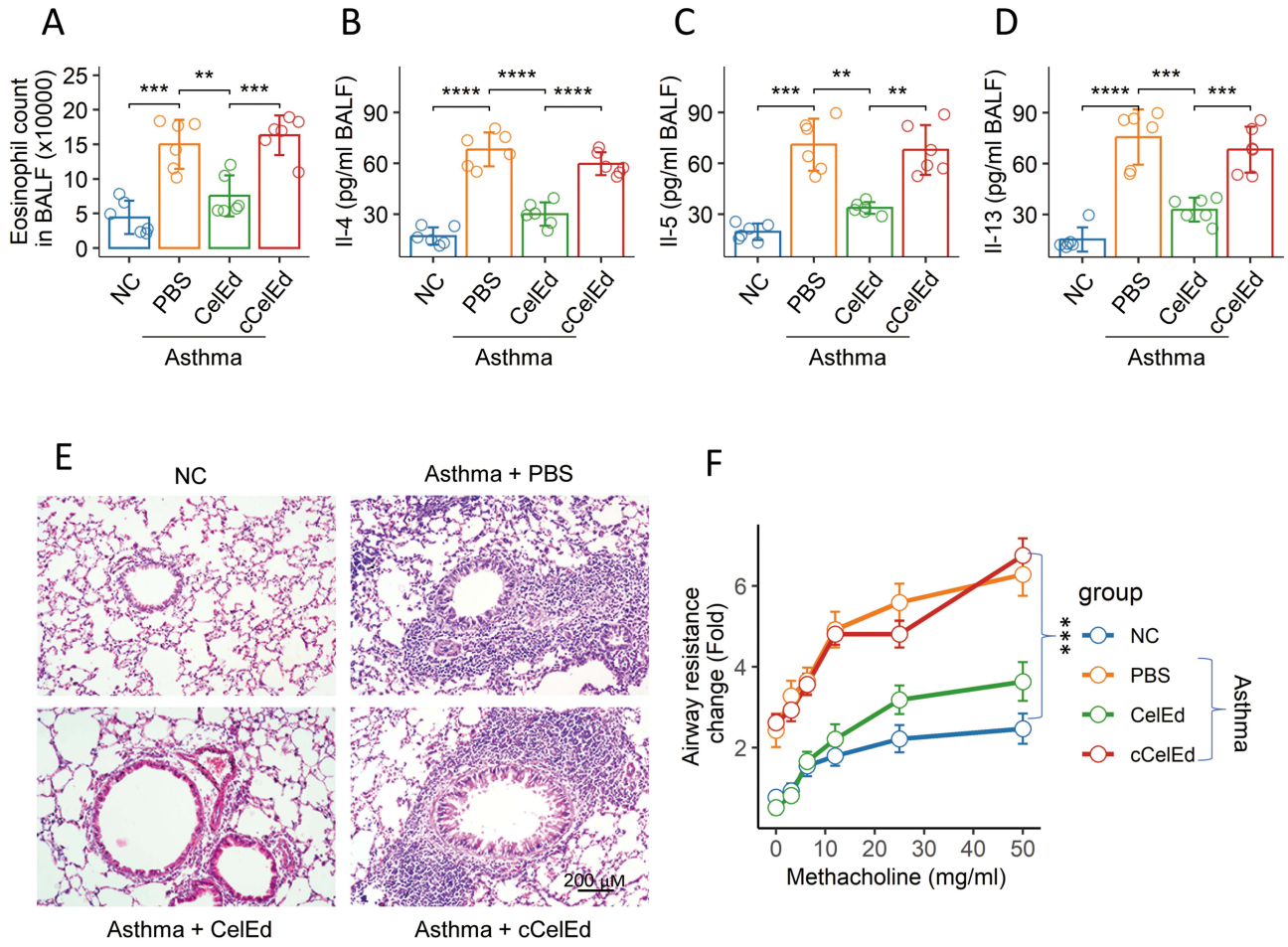

Figure 6 ATF4 modulation alleviates experimental asthma. (**A-D**) BALF parameters: Eosinophil counts (**A**) and Th2 cytokines (B-D). (**E**) Representative H&E-stained lung sections (200×). (**F**) Airway hyperresponsiveness to methacholine. Data from n=6 mice/group presented as mean ± SD with individual points. Statistical analysis: ANOVA with Tukey's test; ***p*<0.01; ****p*<0.001; *****p*<0.0001.

OSM as a Critical Epithelial-Derived Mediator of Allergic Inflammation

The identification of OSM as an epithelial-derived driver of Th2 inflammation extends previous findings implicating OSM in allergic airway remodeling.[18,19] Notably, we demonstrate that:

1. Airway epithelial cells are the primary source of OSM during allergen challenge, with DME inducing 10.85-fold OSM mRNA upregulation;
2. OSM alone recapitulates hallmark allergic features in naïve mice, including 4.3-fold eosinophilia and 7.91-fold IL-13 elevation.This establishes OSM as a causal mediator—rather than a secondary effector—linking epithelial activation to immune polarization. The epithelial origin of OSM is particularly significant, as it positions OSM as an early sensor of allergen exposure, initiating a paracrine signaling cascade to activate downstream immune cells.

Mechanistic Insights: OSM-Driven ERS and the ATF4/Mef2d/GATA3 Transcriptional Axis

Our mechanistic studies reveal a previously uncharacterized pathway by which OSM promotes IL-4 production:

1. ERS Activation in Fibroblasts: OSM triggers PERK-eIF2α phosphorylation (6.8-fold increase), driving ATF4 nuclear translocation (4.8-fold) and ERS gene expression (Perk: 6.2-fold, Eif2a: 5.8-fold);

2. Transcriptional Synergy: ATF4 forms a functional complex with Mef2d, enhancing GATA3 recruitment to the IL-4 promoter. Luciferase assays show 14.09-fold IL-4 promoter activation requiring this tripartite axis;
3. In Vivo Validation: Fibroblast-specific ATF4 knockdown reduces Th2 cytokines by 60–65% and alleviates airway hyperresponsiveness, confirming the axis as a therapeutic target.These findings integrate ERS signaling into the Th2 differentiation program, explaining how epithelial stress signals are translated into immune polarization.

Therapeutic Implications and Translational Potential

The identification of the OSM-ERS-IL-4 axis offers new therapeutic avenues:

- Targeting ERS Signaling: PERK inhibition reduces IL-4 by 73% in vitro, suggesting that ERS modulators could disrupt Th2 polarization;
- Transcriptional Axis Inhibition: ATF4 siRNA nanoparticles attenuate allergic pathology in mice, supporting fibroblast-targeted gene therapy;
- Clinical Relevance: OSM levels correlate with Th2 parameters (r=0.62–0.85), positioning OSM as a potential biomarker for allergic asthma severity.

Study Limitations and Future Directions

This study has several limitations:

1. Murine models may not fully recapitulate human asthma heterogeneity, particularly in genetic and environmental contexts;
2. In vitro fibroblast studies lack the complexity of the airway microenvironment, including immune-cell crosstalk;
3. Long-term safety of ATF4 targeting requires evaluation, given its role in stress responses.

Future studies should

- Validate the OSM-ATF4 axis in human allergic asthma biopsies;
- Explore OSM's role in comorbid allergic diseases (eg, atopic dermatitis);
- Develop small-molecule inhibitors targeting the ATF4/Mef2d interaction or upstream OSM signaling.

Conclusion

This study defines OSM as a critical epithelial-derived mediator of allergic inflammation, uncovering a mechanistic link between epithelial stress, fibroblast ERS, and Th2 polarization. The identification of the ATF4/Mef2d/GATA3 axis provides a framework for developing targeted therapies that disrupt allergic immune responses at the interface of epithelial and mesenchymal cell signaling.

Abbreviations

DME, Dermatophagoides mite extract; OSM, Oncostatin M; ERS, Endoplasmic reticulum stress; BALF, Bronchoalveolar lavage fluid; RT-qPCR, Reverse transcription quantitative polymerase chain reaction; ELISA, Enzyme-linked immunosorbent assay; ChIP, Chromatin immunoprecipitation; siRNA, Small interfering RNA; ATF4, Activating transcription factor 4; GATA3, GATA-binding protein 3; PERK, Protein kinase R-like endoplasmic reticulum kinase; EIF2A, Eukaryotic translation initiation factor 2A; IL-4, Interleukin-4.

Data Sharing Statement

Data are available upon request.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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