

RESEARCH ARTICLE

Topical emollient prevents the development of atopic dermatitis and atopic march in mice

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Abstract

To investigate the effect of emollient on atopic march in a murine model of atopic dermatitis (AD). Following induction of AD with topical calcipotriol (MC903) and ovalbumin (OVA), one group of mice was treated topically with a linoleic acid-ceramide-containing emollient, while mice without emollient treatment served as disease controls. After 28 days, clinical, histological and transcriptomic analyses were performed in the skin lesions and the lung as well as serum cytokine levels. Treatments of mice with MC903 and OVA induced a typical phenotype of AD, accompanied by increased expression levels of Th2 and basophil-related genes in the lung. Topical emollients markedly decreased the severity of skin lesions and inflammatory cell infiltration. Moreover, emollient treatments significantly downregulated expression levels of AD-related genes (286 of 1450 differentially expressed genes), including those related to innate inflammation (*S100a8/a9*, *Il1b*, *Defb3/6*, *Mmp12*), chemokines (*Cxcl1/3*, *Ccl3/4*) and epidermal permeability barrier (*Krt2/6b/80*, *Serp1b12*, *Lce3e*, *Spr2*), etc. Downregulated genes were enriched in mitochondrial OXPHOS-related pathways, while upregulated genes were mainly enriched in axon guidance and tight junctions. Moreover, topical emollient treatments decreased total serum levels of IL-4, along with substantial reductions in IgE and thymic stromal lymphopoietin (TSLP) levels. Furthermore, 187 of 275 upregulated genes in lung tissue were also significantly downregulated, including those involved in leucocyte chemotaxis (*Ccl9*, *Ccr2*, *Retnlg*, *Ccl3*, *Cxcl10*, *Il1r2*, etc.) and basophil activation (*Mcpt8*, *Cd200r3*, *Fcer1a*, *Ms4a2*). In conclusion, topical emollient not only reduces skin inflammation, but also mitigates systemic inflammation by decreasing TSLP and IgE levels. Moreover, topical emollient reduces chemokine production and basophil infiltration and activation in the lung.

KEYWORDS

atopic dermatitis, atopic march, basophils, emollient, RNA sequencing, TSLP

Abbreviations: AA, allergic asthma; AD, atopic dermatitis; AM, atopic march; AR, allergic rhinitis; CCR/CCL, C-C chemokine receptor/ligand; CXCR/CXCL, C-X-C chemokine receptor/ligand; DEGs, differential expressed genes; FcεRI, high-affinity immunoglobulin E (IgE) receptor; GO, Gene Ontology; KEGG, Kyoto Encyclopaedia of Genes and Genomes; La-Cer, linoleic acid-ceramide; OVA, ovalbumin; SEMA4A, semaphorin 4A; OXPHOS, oxidative phosphorylation; TSLP, thymic stromal lymphopoietin.

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1 | INTRODUCTION

The prevalence of allergic diseases, including atopic dermatitis (AD), food allergy, allergic asthma (AA) and allergic rhinitis (AR), has increased significantly worldwide in recent decades, affecting 20%–30% of the world's population.^{1,2} These diseases usually develop in a certain way known as atopic march, starting with AD in early childhood and progress to AA and AR in children.³ Several prospective cohort studies have shown that early AD increases the risk of developing AA (OR 2.06, 95% CI 1.09–3.90) or AR (OR 4.32, 95% CI 2.04–9.12) later in life.^{4,5} Early onset (<2 years), severity, duration (>3 years), presence of barrier-related gene mutations (thymic stromal lymphopoietin [TSLP], filaggrin, etc.) in AD⁶ and high levels of serum IgE are risk factors for the subsequent development of AA or AR.⁷

Epidermal permeability barrier dysfunction and secondary chronic inflammation are two key components in the physiopathology of atopic march. Traditional theory considered that environmental factors (microorganisms, chemicals) and genetic (Filaggrin, tight junction gene defects, etc.) susceptibility led to the disruption of the skin barrier. Upon stimulation, keratinocytes secrete alarmins (IL-25, IL-33, TSLP, etc.) to recruit and activate innate immune cells in the skin, such as basophils⁸ and innate lymphoid cells,⁹ which then activate dendritic cells or Langerhans cells by producing type 2 cytokines. Activated dendritic cells or Langerhans cells take up antigen and migrate to the draining lymph nodes to promote Th2 differentiation. When the sensitized T cells are re-exposed to the allergen through the respiratory and digestive tracts, these T cells secrete large amounts of type 2 cytokines, among which IL-4/13 can disrupt the tight junction of epithelium, promote the antibody class switching to IgE and thus activate mast cells, increase mucin secretion and vascular permeability, while IL-5 induces the chemotaxis of eosinophils.¹⁰ Taken together, a variety of cells and cytokines are involved in the atopic march and that epithelial damage plays a key role in this process.

Emollients are widely used in the basic treatment of AD patients because of their ability to repair the skin barrier and lower the risk of disease recurrence. But whether topical emollients can prevent the atopic march is inconclusive. An Australian clinical randomized controlled trial (RCT) trial showed that using emollient on a daily basis in newborns aged 0–6 months reduced the incidence of AD and food allergy at age 1.¹¹ However, a recent RCT in the UK did not find a reduction in the risk of eczema or food allergy at age 2 after the use of emollient in the first year of life.¹² The aim of the present study was to assess the effect of emollient on AD and later atopic march in a mouse model of AD.

2 | MATERIALS AND METHODS

2.1 | Induction of AD in mice

Specific pathogen free (SPF) grade 6-week-old female C57BL/6 mice were provided by Beijing Vitalriver Laboratory Animal Technology Co. The study protocol was approved by the

Institutional Animal Care and Use Committee (IACUC) of Shanghai Jiao Tong University School of Medicine and was conducted under Chinese National Guidelines (GB/T 35892-20181) for the laboratory animal welfare. Mice were acclimatized to the animal housing environment 1 week prior to the experiment. Mice were randomly divided into the normal controls, AD and AD treated with emollient groups, five mice per group. One day after shaving the back of mice, AD was induced by topical applications of 4 nmol of calcipotriol (MC903, Tocris) solution dissolved in 40 µL of anhydrous ethanol and 200 µg of ovalbumin (OVA, Sigma A5503-1G) solution dissolved in 50 µL of PBS to the back of the mice once daily from Day 1 to Day 11 and from Day 18 to Day 28 (Figure S1). In the emollient-treated group, 60 mg of a linoleic acid-ceramide rich emollient (La-Cer, Dr Yu, China) was applied to the back of mice twice daily, morning after application of MC903 and OVA and evening. The ingredients of the emollient are listed in Table S1. AD mice without emollient treatment served as controls, and mice without any treatment were used as normal controls.

2.2 | Scoring skin lesions

On Day 28, the gross appearance was scored according to a 0- to 3-point scale (0, none; 1, mild; 2, moderate; 3, severe). And the scores of erythema, desquamation, oedema and scratch marks were tallied, with maximal score of 12.

2.3 | Pathohistological analysis

Mouse skin and lung tissue were fixed in 10% formalin solution and embedded in paraffin. Sections (5 µm) were stained with either haematoxylin and eosin (H&E) or toluidine blue staining or immunohistochemical staining of mast cell protease 8 (Mcp8, Biolegend) and observed under a microscope (Olympus). Epidermal thickness was measured using a computerized image analysis system (DP2-BSW).

2.4 | RNA sequencing library construction and analysis

Mouse tissue RNA was extracted using the Eastep Super Total RNA Extraction Kit (Promega, Shanghai), and sequencing libraries were synthesized using the SMARTER mRNA-Seq Library Prep Kit following manufacturer's protocols. The samples were pair-end sequenced using the Illumina sequencing platform to obtain raw data in FASTQ format. Splice removal and quality assessment were performed using FastQC (v0.10.1) software. The raw sequences obtained from sequencing were aligned to the mouse reference genome GRCm38 using Hisat2 (v2.0.1). Sequenced samples with a read alignment rate >80% were used in subsequent analysis. Transcripts were quantified and expression matrices were constructed using the HTSeq

software (v0.6.1). Analysis of differentially expressed genes (DEGs) was performed using DESeq2 package (v1.30.1). Genes were selected using the BH multiple testing correction with a corrected p -value <0.05 and $\log_2$ fold change ≥ 1 . Heatmaps were performed using the ComplexHeatmap package (v2.6.2) for the top 100 absolute values of $\log_2$ fold change up- and downregulated DEGs under different conditions and visualized by ggvenn (v0.1.9) package.

2.5 | KEGG enrichment analysis

The KEGG enrichment analysis was performed using the ClusterProfiler package (v3.18.1) on the DEGs screened between groups and tested based on the hypergeometric test. The p -values were corrected by the BH multiple testing correction. Pathways with q -values <0.2 were defined as significantly enriched pathways. Enrichment results were visualized using the ggplot2 (v3.3.5) package.

2.6 | Cytokine assays

Serum TSLP, IL-4 and IgE levels were measured with respective mouse ELISA kit (Thermo Fisher Scientific) according to the manufacturer's instructions.

2.7 | Real-time fluorescent quantitative PCR (RT-qPCR)

Total tissue RNA was extracted using the Total RNA Extraction Kit (Promega, Shanghai), and cDNA was obtained by reverse transcription, followed by RT-PCR using SYBER Green as a fluorescent marker to detect the expression of *Il-4*, *Tslp* and *Mcpt8* in the tissues. β -actin was used as the internal reference. The results were expressed as $2^{-\Delta\Delta Ct}$. Primers were synthesized by Shanghai Genewiz Co. The primer sequences are listed in Table S2.

2.8 | Statistical analysis

Data were analysed using Graph Prism v8 and represented as mean $\pm$ standard error of the mean (SEM). Comparisons between multiple groups were analysed using one-way analysis of variance (ANOVA) tests, followed by Dunnett's multiple comparisons.

3 | RESULTS

3.1 | Topical emollient reduces OVA+MC903-induced AD-like changes

As expected, repeated applications of OVA+MC903 to the skin induced AD-like skin lesions, including erythema, desquamation, oedema and scratch marks in mice (Figure 1A). The severity of lesions

was significantly decreased following topical applications of the emollient compared to the AD mice (Figure 1A). The histology of AD lesions was characterized by increased skin thickness and inflammatory cell infiltration. Topical emollient largely restored the histological alterations in the skin, evidenced by reductions in epidermal thickening and inflammatory cell infiltration (Figure 1B), particularly mast cells (Figure 1C) and basophils (Figure 1D) in the dermis. Moreover, expression levels of mRNA for Th2-related cytokines such as IL-4, IL-5 and IL-13 were increased in the skin and to a less extent in the lungs of AD mice although the increases were not significant except IL-13 in the lungs ($p < 0.05$) (Figures S2 and S3). Apparently, topical emollient tends to lower expression levels of mRNA for Th2 cytokines, IFN- γ and TSLP in the skin of AD mice, while these cytokines were not altered by emollient in the lungs, which may be due to small range of change and insufficient sample size (Figure S3).

3.2 | Topical emollient downregulates genes associated with mitochondrial oxidative phosphorylation and upregulates genes related to tight junctions

RNA sequencing of the skin showed a total of 2705 DEGs between AD and controls, including 1255 downregulated and 1450 upregulated genes (Figure 2A,B). The upregulated genes included innate immunity and inflammation-related genes such as *S100a8/9*, *Defb6*, *Il1b*, *Cxcl2*, *Ccl3*, *Mmp12*, epithelial alarmin gene *Il1rl1* (*Il33r*), epidermal differentiation- and permeability barrier-related genes such as *Krt2/6b/79*, *Klk8*, *Stfa1/3*, *Serpinb*, *Lce1/3*, *Sprr2* and type II immunity-related genes such as *Il13ra2*, *Mcpt8*, *Chil3*, *Ms4a2* (i.e. *Fcer1b*) (Figure 2A), consistent with the transcriptome features in the lesional skin in AD patients.¹³ The transcriptomic profile of the emollient-treated skin was convergent to that of the controls (Figure 2A). Of the 1450 upregulated genes in the AD group, 286 were significantly downregulated by emollient (Figure 2B). KEGG enrichment analysis showed that downregulated genes induced by emollient were mainly enriched in mitochondrial respiratory chain oxidative phosphorylation (Figure 2C; Table S3). Moreover, emollient treatment upregulated 363 out of the 1255 downregulated genes in the AD group (Figure 2B). Upregulated genes by emollient were enriched in axon guidance and tight junction pathway such as *Plxna1/3* and *Sema4a* (Figure 2C; Table S3), which may be involved in epidermal nerve fibre elongation and regulation of immune cells. These results demonstrate that topical emollient significantly attenuates alterations in epidermal gene expression in AD mice, particularly in those related to oxidative stress and permeability homeostasis.

3.3 | Topical emollient reduces serum TSLP and total IgE levels in AD mice

To determine whether emollient affects systemic inflammation in AD mice, we measured the levels of cytokines and IgE in the serum. Serum levels of Th2 cytokines (TSLP and IL4) and total IgE were

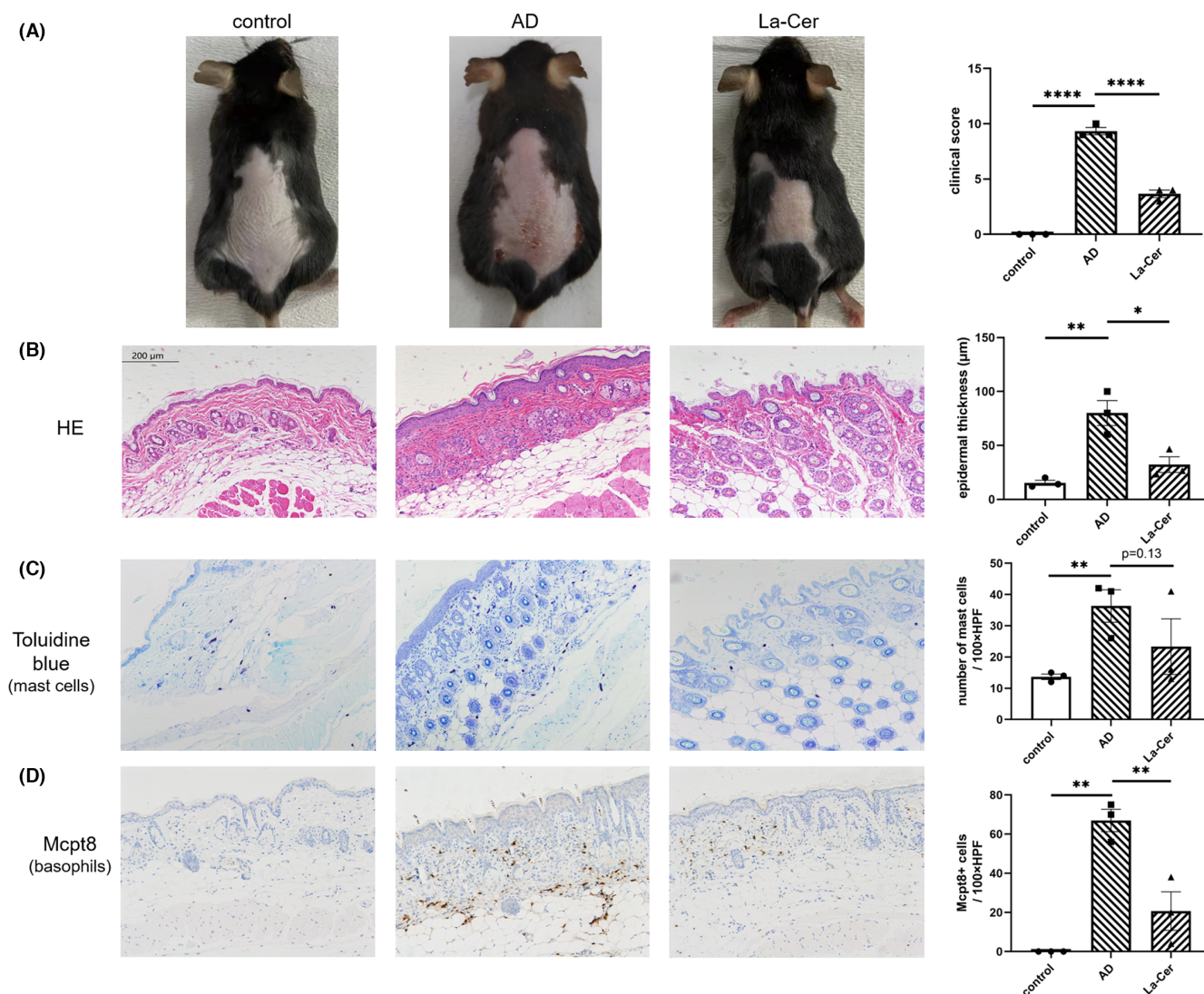


FIGURE 1 Topical emollient prevents the development of atopic dermatitis (AD) in mice. (A) Skin appearance and clinical scores. (B, C) Representative images of histological sections of the skin stained with haematoxylin and eosin (H&E) and toluidine blue, respectively. (D) Mcpt8 staining. Scale bar = 200 μm. Bar graphs show epidermal thickness, number of positive cells per high-power field (100×). Data are represented as mean ± SEM. N = 3–4 mice per group. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$.

higher in AD mice compared to the normal controls. Emollient treatments significantly lowered serum levels of TSLP (AD + emollient vs AD, 15.20 ± 0.90 vs 26.68 ± 4.29 pg/mL) and total IgE (AD + emollient vs AD, 16318 ± 744.5 vs 65249 ± 11530 ng/mL) in AD mice. Serum IL-4 levels were also decreased by topical emollient although the difference was not significant (AD + emollient vs AD, 3.60 ± 0.33 vs 6.50 ± 2.52 pg/mL) (Figure 3).

3.4 | Topical emollient reverses transcriptomic alterations and attenuates basophil-associated gene expression in the lung of AD mice

Because the lung is an important organ in the atopic march, we next assessed whether topical emollient can prevent atopic march. RNA sequencing of lung tissue showed a total of 824 DEGs

between AD and controls, including 418 upregulated genes and 406 downregulated genes. The most significantly changed genes included the basophil-associated protease *Mcpt8*, *Prss34*, basophil surface activation receptor *Cd200r3* and IgE high-affinity receptor *Ms4a2*, suggesting that basophil activation may play a role in the development of atopic march. The transcriptional profile of the emollient-treated mice was similar to that of normal controls (Figure 2D). Of the 418 upregulated genes in AD mice, 229 genes were significantly downregulated by emollient treatment (Figure 2E). GO analysis of these downregulated genes were enriched in leucocyte chemotaxis (Figure 2F), including *Ccl9*, *Ccr2*, *Retnlg*, *Il12a*, *Ccl3*, *Cxcl10*, *Il1r2*. In addition, basophil-related genes were also significantly downregulated by emollient treatment (Figure 2E). Both immunohistochemical staining of the lung and PCR showed significantly higher expression levels of *Mcpt8* in the lung of AD mice, while emollient treatment decreased *Mcpt8*

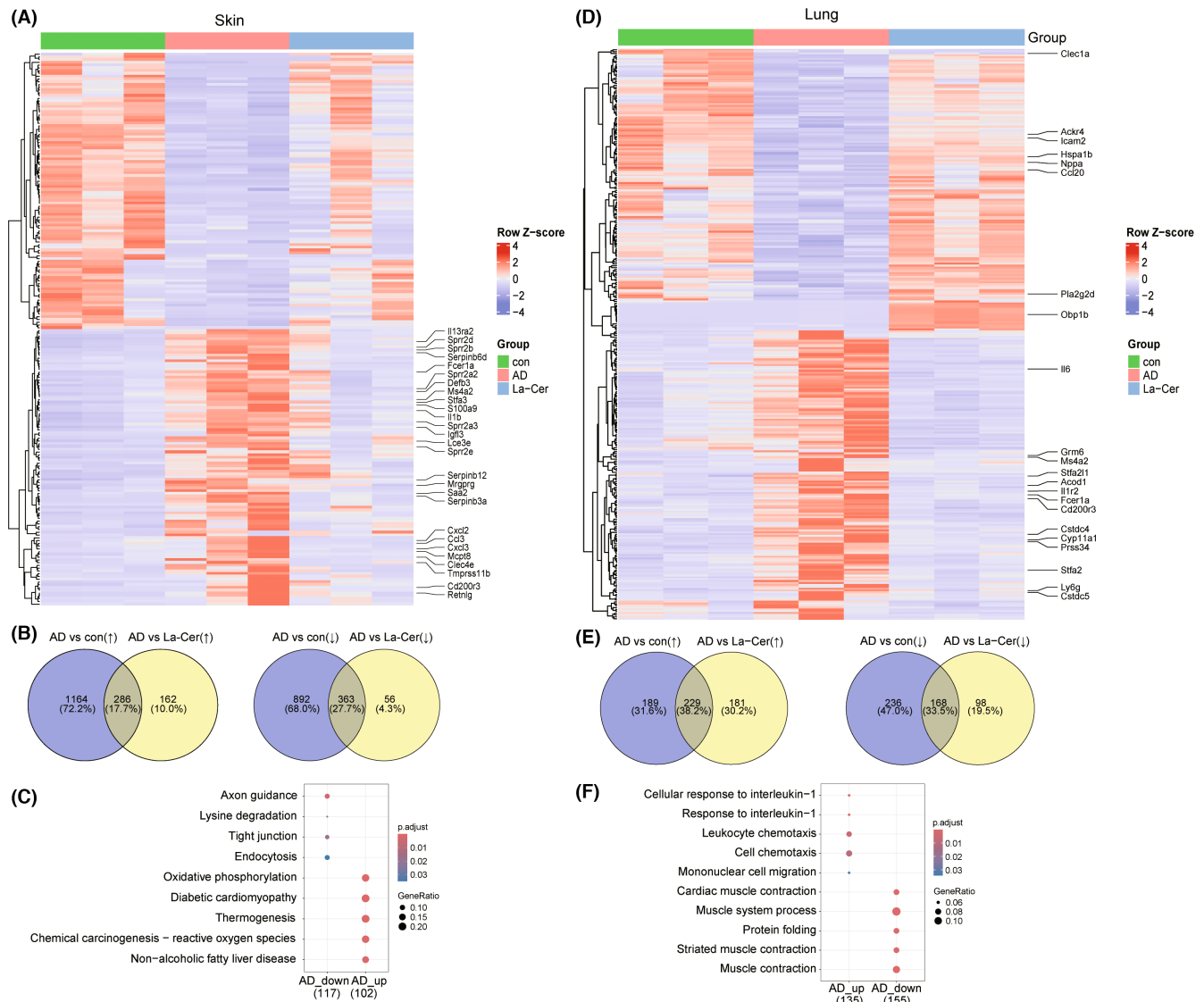


FIGURE 2 RNA sequencing of mouse skin and lung tissue. (A, D) Heat map of cluster analysis of the top 100 differential genes (DEGs) up and down in the atopic dermatitis (AD) and controls in the skin and the lung (green: control group; red: AD group; blue: emollient-treated group). (B, E) Shared gene intersections between DEGs that were both upregulated (or downregulated) in the AD group compared to the control group (blue circles) and the emollient group (yellow circles) in the skin and the lung. (C, F) Enrichment analysis of the gene intersections obtained in (B) and (E) according to terms from Kyoto Encyclopaedia of Genes and Genomes and the Gene Ontology project, respectively. DEGs were defined by $\log_2$ fold change ≥ 1 and corrected p -value < 0.05 .

expression in the lung of AD mice (Figure 4). These results show that topical emollient can reverse transcriptomic alterations in the lung of AD mice, especially reductions in the interaction of chemokines and basophil activation.

3.5 | Correlation analysis between DEGs in the skin and the lung as well as biomarkers and clinical scores

As shown in Figure 5, genes in the skin that are associated in epidermal barrier, protease inhibitors (e.g. *Serpina/b*, *Stfa*, *Spr2*, *Krt* family), oxidative phosphorylation, type II immunity and leucocyte migration

were positively correlated with each other. Allergic, inflammatory, basophil genes in the lung (e.g. *Stfa211*, *Fcer1a*, *Cstcd4*, *Ms4a2*, *Stfa2*) were positively correlated with genes related to epidermal barrier, protease inhibitors, oxidative phosphorylation, type II immunity, serum type II cytokines and clinical scores. The highest correlations were found between allergy/inflammation genes in the lung and leukocyte chemotaxis/innate immunity in the skin, suggesting an important role of the cutaneous function in the development of atopic march.

Tight junction protein and neurodevelopment-related genes (e.g. *Sema4a*, *Plxna* family) in the skin were negatively correlated with other pathway-associated genes (e.g. skin: *Serpmb*, *Cox5b*, *Ndufa4*, *Il1r1*, *Defb6*/*Il1b*; lung: *Mmp8*).

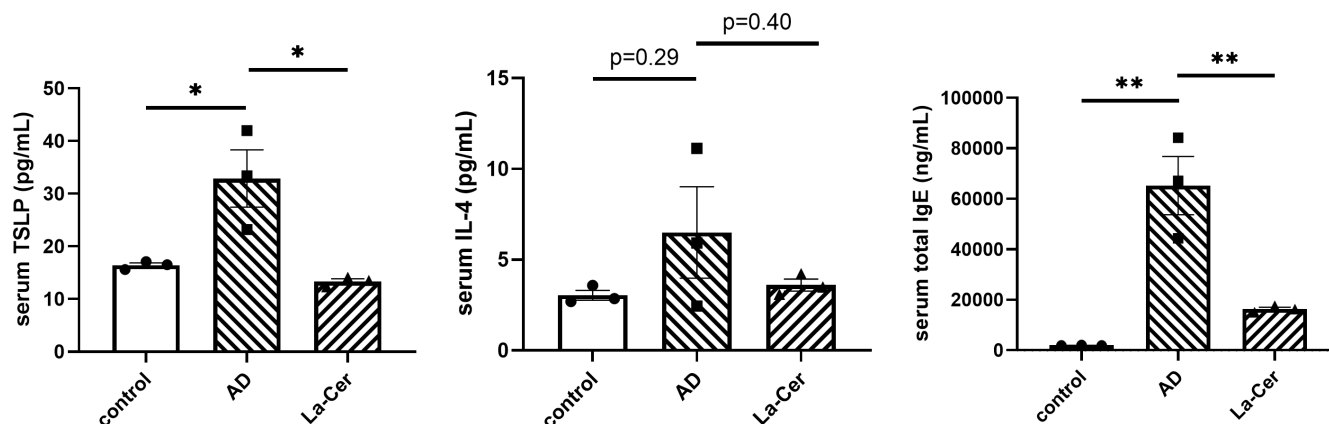


FIGURE 3 Topical emollient reduces serum thymic stromal lymphopoietin (TSLP) and IgE levels in atopic dermatitis (AD) mice. The serum TSLP, IL-4 and total IgE levels were measured by ELISA. Data are shown as mean $\pm$ SEM. $N=3-4$ mice per group. * $p < 0.05$, ** $p < 0.01$.

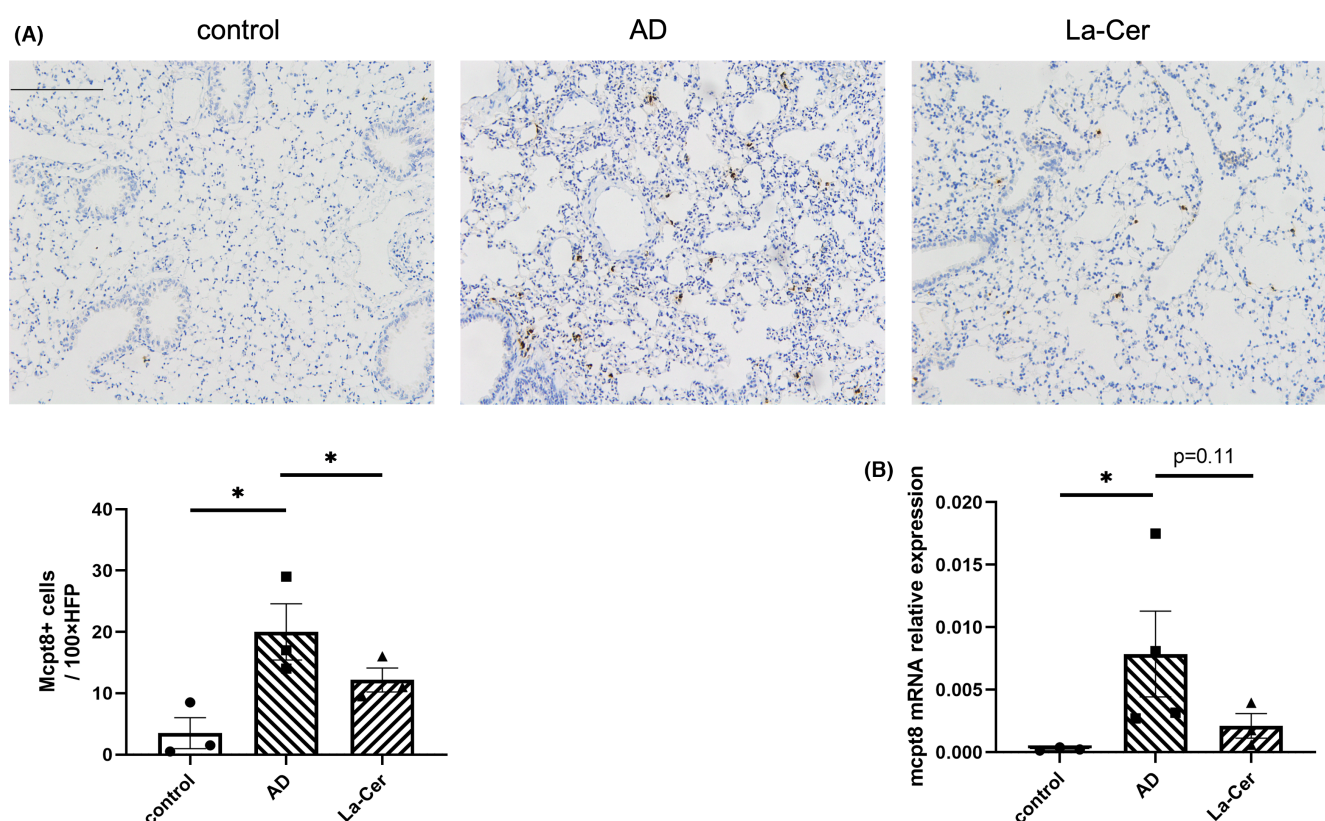


FIGURE 4 Topical emollient downregulates basophil-associated gene expression in the lung. (A) Immunohistochemical staining of Mcpt8, a marker of basophils. Scale bar = 200 μ m. The bar graph shows the number of Mcpt8-positive cells per high-power field (100 $\times$). (B) Expression of Mcpt8 mRNA in the lung (RT-qPCR). Data are represented as mean $\pm$ SEM. $N=3-4$ per group. * $p < 0.05$.

4 | DISCUSSION

AD can be a precedent of the atopic march. Early-onset AD is usually more severe and persistent, representing a risk factor for asthma development.^{4,14} In addition, patients with AD are more likely to develop food sensitization than healthy controls with an OR (odd ratio) up to 6 at 3 months of age.¹⁵ Thus, early intervention of AD can be critical to prevent infants from developing lifelong chronic atopic diseases and reduce disease burden. Although biological agents

and other immune suppressors can effectively alleviate AD,^{16,17} the unaffordable cost and severe adverse reactions limit their usage in clinical setting. However, evidence suggests that topical emollients can improve AD and prevent the development of atopic march.¹¹ Correspondingly, we demonstrated here that topical emollient attenuated the development of AD and atopic march in a mouse model of OVA+MC903-induced AD.

Although the precise underlying mechanisms by which topical emollient mitigates the development of AD and atopic march



FIGURE 5 Correlation analysis of emollient-regulated genes in the skin and lung. Genes' names are listed on the left with 's' indicating genes in the skin and 'l' indicating genes in the lung.

are not clear, evidence suggests the involvements of the following mechanisms in the action of emollient. First, epidermal dysfunction is attributed to development of AD.¹⁸ Accordingly, improvement in epidermal function by topical emollient alleviates AD in both humans and murine models.^{19,20} Moreover, topical emollient, same one used in the present study, improves epidermal permeability barrier and stratum corneum hydration in humans.²¹ Therefore, improvement in epidermal function is one mechanism by which emollient attenuated AD and atopic march. The emollient-induced improvement in epidermal function is likely attributable to the upregulation of genes related to epidermal differentiation and lipid production because the omega-6 linoleic acid in the emollient can activate peroxisome proliferator-activated receptor alpha.²² Second, in comparison to normal skin, AD skin exhibits lower expression levels of Sema4A gene, a family member of semaphorins involved in the nervous and immune systems. Sema4A is a membrane-bound protein secreted by

dendritic cells and Th1 cells. Mice with Sema4A deficiency exhibit features of AA, and exogenous supplementation of Sema4A can directly or indirectly benefit AA by inhibiting the Th2 response through Tim2.²³ We showed here that topical emollient upregulated expression levels of Sema4A genes. In contrast, topical emollient downregulated other immune-related genes, including pro-inflammatory genes (*Il1b*, *Cxcl1*), Th2 pathway (*Il13ra2*, *Fcgr1A*), and serum levels of TSLP and total IgE. Both TSLP and total IgE play an important role in the pathogenesis of atopic march. TSLP, an IL-7-like cytokine expressed in epithelial tissues, can induce Th2-type responses and is involved in a variety of allergic diseases. Overexpression of epithelial-derived TSLP can induce or exacerbate AD or asthma-like phenotypes in mice.^{24,25} In contrast, knockdown of TSLP blocks the development of allergic disease.²⁶ Moreover, TSLP can stimulate basophils to rapidly infiltrate inflammatory sites and collaborate with dendritic cells to promote Th2 differentiation.⁸ IL-3 can stimulate basophil

degranulation and histamine production in response to FCER1 cross-linking signals.²⁷ Thus, it is likely that TSLP induces basophil proliferation, activation and infiltration into the lung, causing microinflammation. When the allergen is encountered again, FCER1 cross-linking induces basophil activation to produce IL-4 and interacts with innate lymphoid cells and dendritic cells to cause Th2 drift in the lung environment, triggering the development of the atopic march. Additionally, multiple sensitization and high IgE levels are strongly linked to the development of AA and AR from AD.^{7,28} Hence, upregulation of Sema4A and downregulation of TSLP and total IgE are another mechanism by which topical emollient benefits AD and atopic march.

Finally, although basophils make up <1% of peripheral blood leukocytes, they can produce large amounts of Th2-type cytokines (including IL-4) early in the development of allergic disease.^{29,30} In an asthma model, knockdown of IL-4 in basophils results in significant reduction in innate lymphoid cells 2 in the lungs of mice, suggesting essential role of basophil-produced IL-4 in the expansion of innate lymphoid cells 2 in vivo.³¹ In the lungs of AD mice, basophils and their related genes, including basophil proteases *Mcpt8* and *Prss34* (i.e. mast cell protease-11) and their surface activation receptors *Cd200r3* and *Ms4a2* (i.e. *Fcer1b*), were upregulated, while topical emollient decreased the number of basophils and downregulated basophil-related genes. Thus, reductions in the number of basophils and basophil-related gene expression can also account for additional mechanism by which topical emollient attenuate AD and atopic march.

In summary, topical emollient exhibits multiple benefits in a mouse model of AD, including inhibition of inflammation, mitigation of atopic march and modulation of neuroimmune function in the skin and the lungs. Although benefits of topical emollients in AD have been well documented in clinical setting, whether atopic march can be prevented by topical emollient in humans remains to be explored.

AUTHOR CONTRIBUTIONS

Conceptualization and design of experiments was done by Xiaopan Wang, Jiayi Zhang and Jie Zheng. Experiments were performed by Jiayi Zhang, Li Zhang, Mengyan Hu. Analysis of the data was done by Xintian Xu, Li Zhang. The draft of the manuscript was prepared by Jiayi Zhang and reviewed by Lihong Chen, Yunchen Le and Jie Zheng. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE222019>.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1

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