Arthritis Research & Therapy

RESEARCH Open Access

Oxysterols contribute to immune cell recruitment in SLE skin lesions

Xiaoyun Chen[1], Lianlian Ouyang[4], Sujie Jia[2,3*] and Ming Zhao[1,2,3*]

Abstract

Background Abnormal oxysterol metabolism has been observed in the peripheral blood of SLE patients, but its role in systemic lupus erythematosus (SLE) skin lesions remains unclear.

Methods Targeted oxidized lipid metabolomics analysis using liquid chromatography-mass spectrometry (LC-MS) was performed to quantify oxysterols in SLE skin lesions. Immunohistochemical staining and single-cell sequencing data analysis confirmed the upregulation of oxysterol-encoding enzymes CH25H and CYP7B1. The impact on fibroblast-mediated PBMCs chemotaxis was assessed using a transwell chamber.

Results We identified aberrant oxidized cholesterol metabolism in SLE skin lesions, characterized by elevated levels of 7-ketocholesterol, 5α-6α-cholestane-3β,5α,6β-triol, and so on. Fibroblasts were the primary cells expressing oxysterol-encoding genes, with CH25H and CYP7B1 expression upregulated via the IL-1β-mediated p38 MAPK and NFκB pathways. Notably, IL-1β-stimulated fibroblasts demonstrated enhanced PBMCs recruitment, which was attenuated by a GPR183 inhibitor.

Conclusion Our findings reveal a potential mechanism by which fibroblasts contribute to immune cell recruitment in SLE skin lesions by expression of CH25H and CYP7B1. This study underscores the significance of oxysterol metabolism in SLE skin lesion pathogenesis and highlights potential therapeutic targets for SLE skin lesion treatment.

Introduction

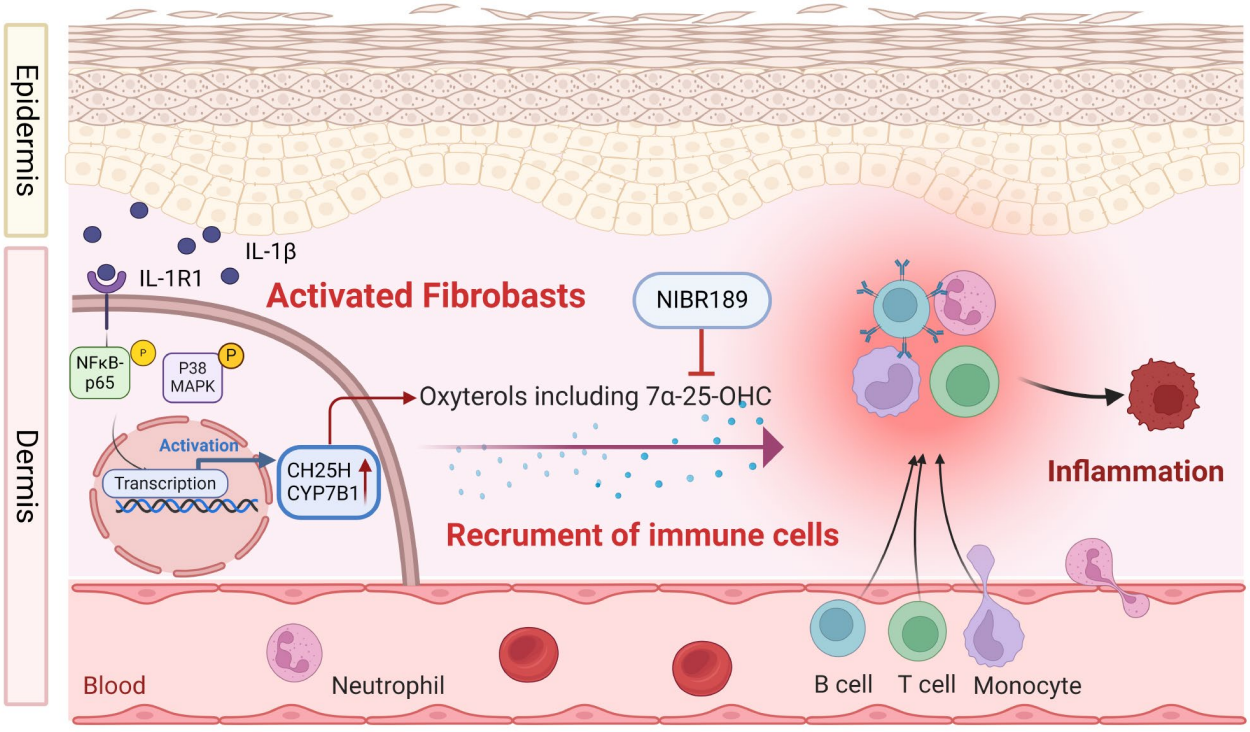
Lupus erythematosus is a chronic autoimmune disease that predominantly affects the skin, with most patients experiencing skin involvement [1]. Previous studies have demonstrated that dendritic cell activation and tolerance changes lead to abnormal inflammatory mediator production, particularly type I interferons, which mediate innate and adaptive immune abnormalities [2]. Effector T cells and Treg lose balance, and B cells continuously produce autoantibodies, leading to the continuous expansion of the autoimmune pathogenesis in SLE [2]. However, the mechanisms underlying immune cell aggregation, migration, and regulation remain unclear.

Fibroblasts are important cells in the skin and are the stromal cells that come into contact with various immune cells. Fibroblasts respond to different stimuli and exhibit different functions [3]. Recent studies have emphasized the important role of fibroblasts in recruiting immune cells. In vitiligo, fibroblasts recruit $CD8^+$ T cells through CXCL9 and CXCL10 to participate in melanocyte killing [4], and in specific skin inflammation, fibroblasts recruit neutrophils by producing CXCL12 [5]. However, it remains unclear how fibroblasts participate in recruiting

*Correspondence:
Sujie Jia
sujiejia@126.com
Ming Zhao
zhaoming301@pumcderm.cams.cn

Full list of author information is available at the end of the article

Graphical abstract



Rheumatology key messages

- SLE skin lesions show abnormal oxysterol metabolism, with fibroblasts being the main source of increased CH25H and CYP7B1 genes.
- IL-1β-mediated p38 MAPK and NFκB pathways implicated in CH25H and CYP7B1 upregulation.
- Enhanced PBMCs recruitment by IL-1β-stimulated fibroblasts can be attenuated by a GPR183 inhibitor, offering potential SLE skin lesion treatment.

Keywords Systemic lupus erythematosus, Fibroblasts, Oxyterols, CH25H, CYP7B1

immune cells, particularly T cells and B cells in lupus skin lesions.

Oxysterols, a crucial class of cholesterol derivatives, have been implicated in the onset and progression of various diseases [6–8]. Accumulating evidence indicates that SLE patients exhibit widespread lipid metabolism abnormalities [9, 10]. 7α-25-OHC, an important oxysterol, can contribute to disease progression by recruiting immune cells [11–13]. While fibroblasts have been shown to promote autoimmune disease progression by secreting inflammatory factors and chemokines, it is unclear whether fibroblasts secrete oxysterols to participate in disease progression.

In this study, we assessed oxidized lipid expression in lupus skin lesions and observed abnormally increased oxysterols. Fibroblasts were found to specifically express CH25H and CYP7B1, genes that mediate 7α-25-OHC production, a unique and important oxysterol. We identified IL-1β as a crucial cytokine promoting CH25H and CYP7B1 upregulation in fibroblasts, with p38 MAPK and NFκB-p65 involved in regulation. IL-1β upregulation in lupus skin lesions was also confirmed. 7α-25-OHC promotes immune cell migration via GPR183, enhancing fibroblast-immune cell cross-talk and immune cell infiltration in skin lesions. GPR183 inhibition weakens fibroblast chemotactic effects on immune cells. Thus, we propose that fibroblasts may contribute to lupus skin lesion formation by releasing oxysterols and promoting local immune cell infiltration, accelerating disease progression.

Methods and materials

Mice and sections

MRL/MpJ and MRL/Lpr mice were acquired from SiPeiFu. They were housed under specific pathogen-free (SPF) conditions. Skin samples from both mice were collected from MRL/MpJ and MRL/Lpr mice. Human skin biopsies were obtained from the Second Xiangya

Hospital of Central South University. This study was approved by the Ethics Committee of Second Xiangya Hospital, Central South University.

Cell culture and stimulation

We isolated primary dermal fibroblasts from healthy individuals by digesting skin tissue with Dispase II enzyme and type II collagenase. The resulting single-cell suspension was seeded into TC culture flasks and cultured until confluence before passaging. The fibroblasts were maintained in DMEM supplemented with 10% Gibco FBS and 1% penicillin-streptomycin. Primary fibroblasts between passages 3 and 10 were used for experiments. Fibroblasts were pretreated with starvation prior to the addition of various stimuli such as IL-1β (10 ng/mL) for 24 h. The following inhibitors were utilized: ML120B (30 μM, Selleck, S7736) for inhibition of the NFκB pathway, S1076 (10 μM, Selleck) for inhibition of p38 MAPK, S7101 (10 μM, Selleck) for inhibition of ERK1/2, S2789 (10 μM, Selleck) for inhibition of JAK3, and S1460 (10 μM, Selleck) for inhibition of JNK. Subsequently, the cells were collected for further analysis.

Oxidized cholesterol metabolites

Skin lesions and adjacent non-lesional skin were obtained from three age-matched MRL/Lpr mice. Lipids were extracted from the tissues using a modified Bligh and Dyer method. In brief, the sample was incubated with 500 μL of 1 N potassium hydroxide in ethanol containing 5 μg of butylated hydroxytoluene (BHT) as an internal standard at 37 °C and 1200 rpm for 1 h. After incubation, 250 μL of MilliQ water and 1 mL of hexane were added to the sample. The mixture was then vortexed and centrifuged at 4 °C and 12,000 rpm for 5 min. The upper hexane phase containing oxysterols and cholesterol was transferred to a new EP tube. The extraction was repeated once more, and the combined extracts were dried in organic mode using a SpeedVac. The pooled extract was dried in a SpeedVac under organic mode. Oxysterols and sterols were derivatised to obtain their picolinic acid esters prior to LC/MS analysis on a Thermofisher U3000 DGLC coupled to Sciex QTRAP 6500 Plus, and quantitated by referencing to the spiked internal standards as previously described.

Single cell sequencing data analysis

Single-cell sequencing data for skin samples from healthy controls (HC) and SLE patients were obtained from our research group's previous study [14], available in the GEO database (GSE179633). The Seurat package was utilized for single-cell RNA sequencing analysis, and differentially expressed genes (DEGs) for each cluster were identified using the Find All Markers function. Fibroblasts were identified by the expression of COL1A1 and COL3A1 genes, and their distribution was visualized using t-distributed Stochastic Neighbor Embedding (t-SNE) plots. Feature plots and stacked violin plots were used to display specific gene expression levels. Additional R packages, such as ggplot2 and dplyr, were employed for data visualization.

Statistical analysis

GraphPad Prism 9.0 was used to perform statistics. *ns*, no significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$. Data are presented as mean ± SEM, and statistical significance was assessed using paired or unpaired t-tests, ordinary one-way ANOVA, or two-way ANOVA, as appropriate.

Detailed methods are provided in the Supplementary Material 2.

Results

Oxyterol abnormalities in lupus skin lesions

The pathogenesis of systemic lupus erythematosus (SLE) has increasingly been linked to lipid and cholesterol metabolism aberrations [15, 16], however, the understanding of these processes in SLE skin lesions remains limited. We conducted a targeted oxidized lipidomics analysis on lesional and non-lesional skin samples from age-matched MRL/Lpr mice (Fig. 1A). Our data demonstrated a significant elevation of sterol levels in the lesional skin of MRL/Lpr mice compared to non-lesional skin (Fig. 1B, Supplementary Material 1).

Consistent with previous observations in the plasma of lupus patients, we detected substantially higher levels of various oxysterols in the lesional skin of MRL/Lpr mice relative to non-lesional skin. These oxysterols included desmosterol/zymosterol, dehydrocholesterol, 4β-hydroxycholesterol, 6α-hydroxy-5α-cholestanol, 5α,6α-epoxycholesterol, 5α,6β-epoxycholesterol, 7-ketocholesterol, and 5α-cholest-8(14)-ene-3β,15α-diol (Fig. 1C). Although FF-MAS, T-MAS, and 24-OH-CHO showed a trend toward elevation, these differences did not reach statistical significance, potentially due to the limited sample size (Supplementary Material 4, Fig. S1).

Elevated expression of CH25H and CYPB1 in fibroblasts from lupus skin lesions

To elucidate the underlying cause of increased oxysterols in SLE skin lesions, we examined the expression of enzymes involved in cholesterol metabolism, including Ch25h, Cyp7b1, Hsd3b7, Cyp39a1, and Cyp46a1. Our results showed that Cyp39a1, Cyp46a1, and Hsd3b7 did not change significantly in MRL/Lpr skin lesions, while Ch25h and Cyp7b1 were significantly upregulated (Fig. 2A). Immunohistochemical staining confirmed the upregulation of Ch25h and Cyp7b1 in MRL/Lpr skin lesions compared to MRL/MpJ skin (Fig. 2B-C). To

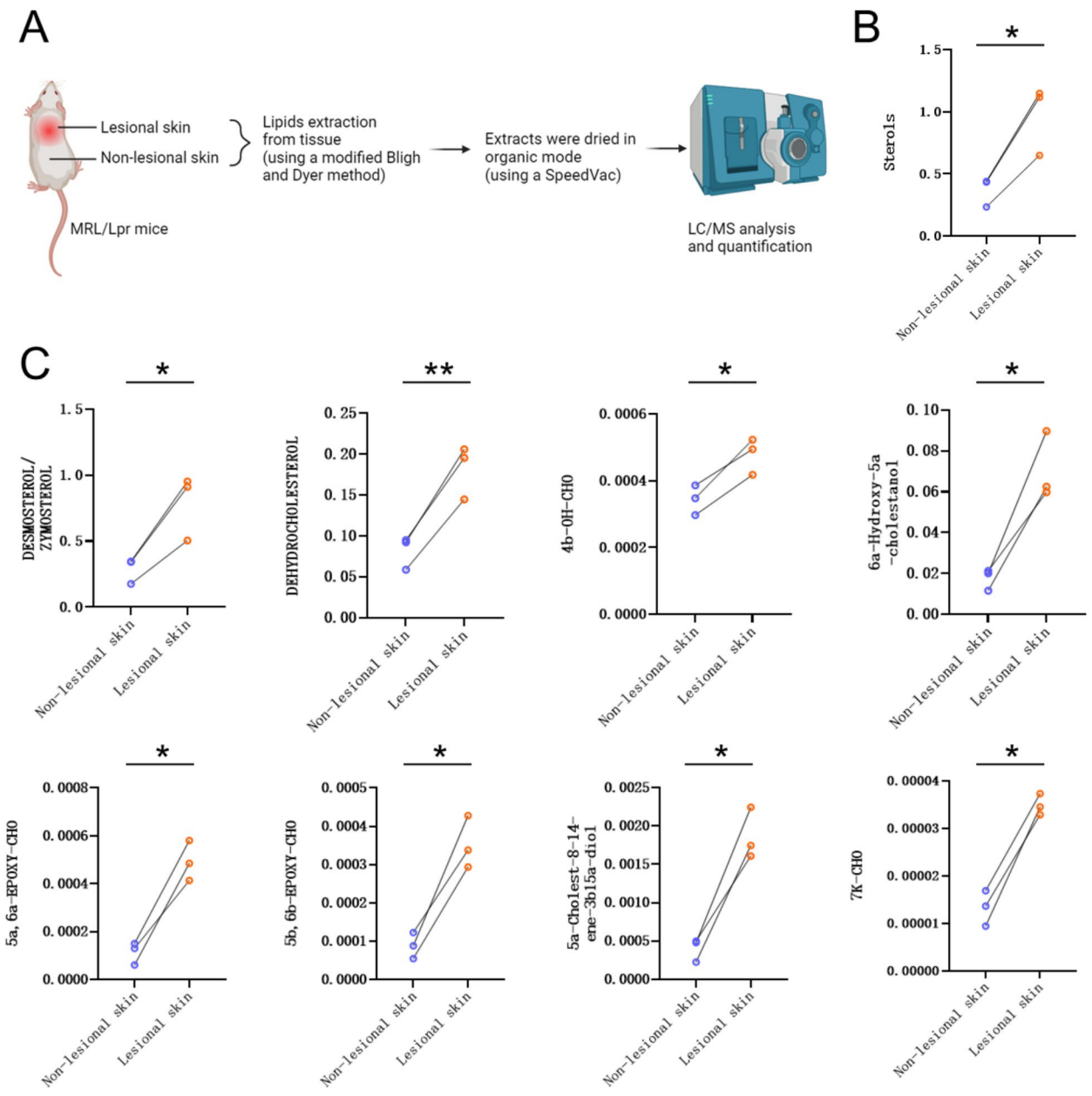


Fig. 1 Oxysterols were increased in SLE skin lesions. (**A**) Process flowchart for targeted lipidomics analysis (n = 3). (**B**) Paired t-test line graph showing the significant difference in sterol levels between the lesional skin and non-lesional skin of MRL/Lpr mice ($p = 0.0234$) (n = 3). (**C**) Paired t-test line graphs displaying the significant differences in oxysterols levels between the lesional skin and non-lesional skin of MRL/Lpr. The graphs include desmosterol/zymosterol ($p = 0.0288$), dehydrocholesterol ($p = 0.0064$), 4β-hydroxycholesterol ($p = 0.0227$), 6α-hydroxy-5α-cholestanol ($p = 0.0278$), 5α,6α-epoxycholesterol ($p = 0.0156$), 5α,6β-epoxycholesterol ($p = 0.0202$), 5α-cholest-8(14)-ene-3β,15α-diol ($p = 0.0166$) and 7-ketocholesterol ($p = 0.0066$) (n = 3). The p values were calculated using paired t test. LC/MS: liquid chromatography-mass spectrometry

determine whether these changes also occur in human skin, we performed immunohistochemical staining on SLE skin lesions and normal human skin. Our findings revealed increased expression of CH25H and CYP7B1 in SLE skin lesions (Fig. 2D-E).

We observed that CH25H and CYP7B1 staining was primarily localized in the dermis, rather than the epidermis. To further identify the cells expressing CH25H and CYP7B1, we analyzed single-cell sequencing data from the dermis of SLE and normal human skin. Our analysis revealed that fibroblasts specifically expressed high levels of cholesterol oxidation metabolism-related genes CH25H and CYP7B1, with a prominent expression peak (Fig. 3A). Further analysis indicated that the $CXCL1^{+}$ fibroblast subpopulation predominantly expressed CH25H and CYP7B1 (Fig. 3B), and these expressions

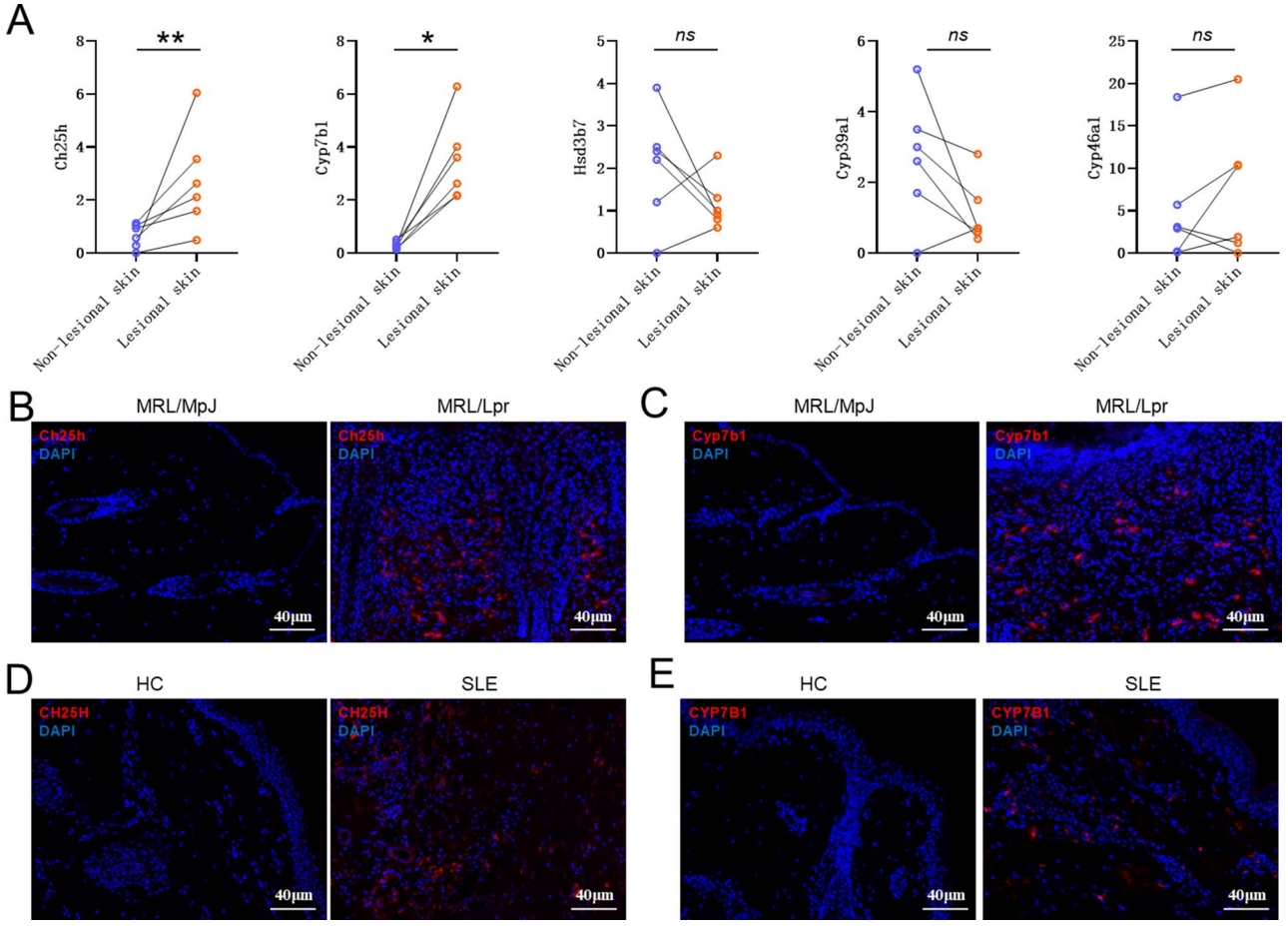


Fig. 2 Upregulation of CH25H and CYP7B1 expression in SLE skin lesions. (**A**) Paired t-test line graphs showing the RT-qPCR analysis of Ch25h ($p = 0.0490$), Cyp7b1 ($p = 0.0043$), Hsd3b7, Cyp39a1, and Cyp46a1 genes in lesional skin and adjacent non-lesional skin in MRL/Lpr mice (n = 6). (**B**-**C**) Representative immunohistochemistry images of skin from MRL/MpJ (left) and MRL/Lpr (right) mice, showing increased expression of Ch25h (**B**) and Cyp7b1 (**C**) in MRL/Lpr skin (n = 3). (**D**-**E**) Representative immunohistochemistry images of skin from healthy control (HC, left) and SLE (right) patients, showing increased expression of CH25H (**D**) and CYP7B1 (**E**) in SLE lesional skin (n = 3). The data shown were representatives of three independent experiments. The *p* values were calculated using paired t test (**A**)

were significantly elevated in SLE and DLE skin lesions compared to normal skin (Fig. 3C). These findings suggest that CH25H and CYP7B1 are primarily expressed by fibroblasts, specifically the $CXCL1^+$ subpopulation, in lupus skin lesions.

IL-1β regulates CH25H and CYP7B1 expression in fibroblasts and recruitment of $GPR183^+$ immune cells

CH25H and CYP7B1 are critical enzymes responsible for producing 7α-25-OHC [17], a specific type of oxysterol that has been shown to recruit $GPR183^+$ immune cells and play significant roles in various immune diseases. We detected a large number of $GPR183^+$ cells in SLE skin lesions via immunohistochemistry (Fig. 4A), and a similar increase in $Gpr183^+$ cells was observed in MRL/Lpr mice (Fig. 4B). Therefore, we hypothesized that fibroblasts in SLE skin lesions could promote immune cell recruitment by upregulating CH25H and CYP7B1 to recruit $GPR183^+$ immune cells. We analyzed GPR183 expression in SLE skin lesions and found that dermal immune cells, including T cells, B cells, and macrophages, expressed GPR183 (Supplementary Material 4, Fig. S2A). Although epidermal immune cells also expressed GPR183, there was no significant expression or upregulation of CH25H and CYP7B1 detected in the epidermis (Supplementary Material 4, Fig. S2B). Additionally, we analyzed $GPR183^+$ immune cells in SLE skin lesions and found that GPR183 was co-expressed by both $CD3^+$ T cells and $CD19^+$ B cells (Fig. 4C), suggesting a potential role for these cells in the pathogenesis of SLE skin lesions.

To investigate the factors leading to increased CH25H and CYP7B1 expression in fibroblasts, we treated primary human fibroblasts with various cytokines. Our results confirmed that human dermal fibroblasts express higher levels of CH25H and CYP7B1 in response to cytokines such as IL-1β and IL-17A, with IL-1β eliciting the strongest response (Fig. 4D). We then evaluated the chemotactic effect of supernatants from control and

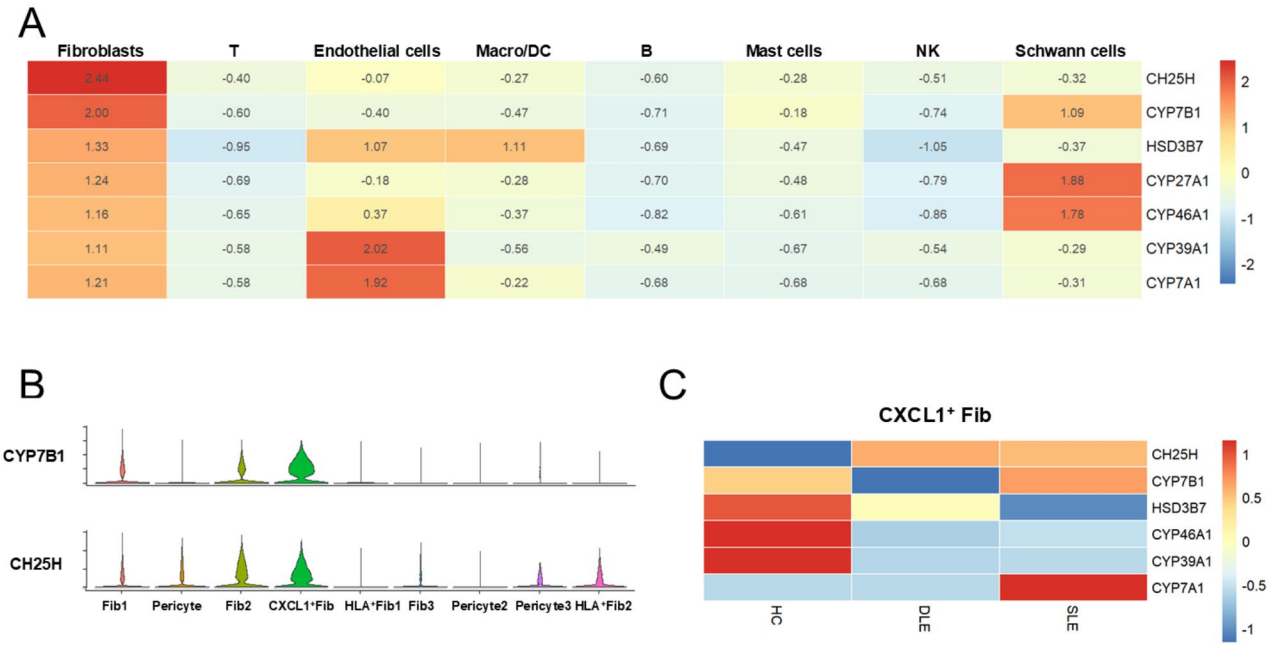


Fig. 3 Enhanced expression of CH25H and CYP7B1 in fibroblasts revealed by single-cell sequencing data. **(A)** Heatmap showing the expression levels of oxysterol-related enzyme genes in different cell subtypes from the dermis of lupus skin lesions. Fibroblasts show high expression levels of CH25H and CYP7B1.(**B**)Violin plot showing the expression levels of CH25H and CYP7B1 in fibroblast subsets. CXCL1$^+$ fibroblasts show the highest expression levels of CH25H and CYP7B1. (**C**) Heatmap showing the differential expression of CH25H, CYP7B1, HSD3B7, CYP46A1, CYP39A1, and CYP7A1 in CXCL1$^+$ fibroblasts from healthy controls, DLE, and SLE patients. Macro: Macrophage; DC: dendritic cells; SLE: systemic lupus erythematosus; DLE, discoid lupus erythematosus

IL-1β-stimulated fibroblasts on PBMCs as shown in Fig. 4E. The supernatant from IL-1β-stimulated fibroblasts significantly enhanced the chemotactic effect on PBMCs. To further confirm whether this chemotactic effect is mediated via the oxysterol-GPR183 pathway, we added NIBR189, a GPR183 blocker into the supernatants. Upon treatment with NIBR189, we observed a significant reduction in the chemotactic effect, which strongly indicates that the recruitment of immune cells is indeed mediated through the oxysterol-GPR183 pathway (Fig. 4F).

IL-1β has been implicated in the pathogenesis of cutaneous lupus erythematosus (CLE), and dermal fibroblasts are among the skin cells expressing the highest levels of IL-1R and exhibiting the most robust response to IL-1β stimulation [18–20]. We confirmed increased IL-1β expression in lupus skin lesions using immunohistochemical staining (Fig. 4G-H).

NFκB and p38 MAPK contribute to the upregulation of CH25H and CYP7B1

IL-1β can lead to NFκB activation and nuclear translocation [21]. In order to investigate the involvement of NFκB in regulating CH25H and CYP7B1, we stimulated fibroblasts with IL-1β in the presence or absence of ML120B, an NFκB inhibitor. Our results demonstrated that the upregulation of CH25H and CYP7B1 in IL-1β-treated dermal fibroblasts was significantly inhibited by blocking the NFκB signaling pathways (Fig. 5A-B). To further elucidate the specific component of the NFκB pathway involved in this regulation, we transfected cells with siRNA-NFκB-p65 or siRNA-NFκB1. Our results showed that IL-1β-induced upregulation of CH25H and CYP7B1 was dependent on NFκB-p65, as siRNA-NFκB-p65 transfection abolished the upregulation, while si-RNA-NFκB1 had no such effect (Fig. 5C-D). These findings suggest that NFκB-p65 is a crucial component of the NFκB pathway involved in regulating CH25H and CYP7B1 expression in dermal fibroblasts.

We also treated fibroblasts with various pathway inhibitors, including a broad-spectrum JNK inhibitor, JAK3 inhibitor, ERK1/2 inhibitor, and p38 MAPK inhibitor. Our results showed that the p38 MAPK inhibitor could partially inhibit the expression of CH25H and CYP7B1. However, the other inhibitors did not have significant effects (Supplementary Material 4, Fig. S3A-B). Furthermore, we confirmed that the expression of p-NFκB-p65 and p-p38 MAPK was increased in IL-1β-stimulated fibroblasts using western blot analysis (Fig. 5E-F, Supplementary Material 3). These findings suggest that the NFκB-p65 and p38 MAPK pathways are activated and crucial for IL-1β-mediated expression of oxysterol-related genes in human dermal fibroblasts.

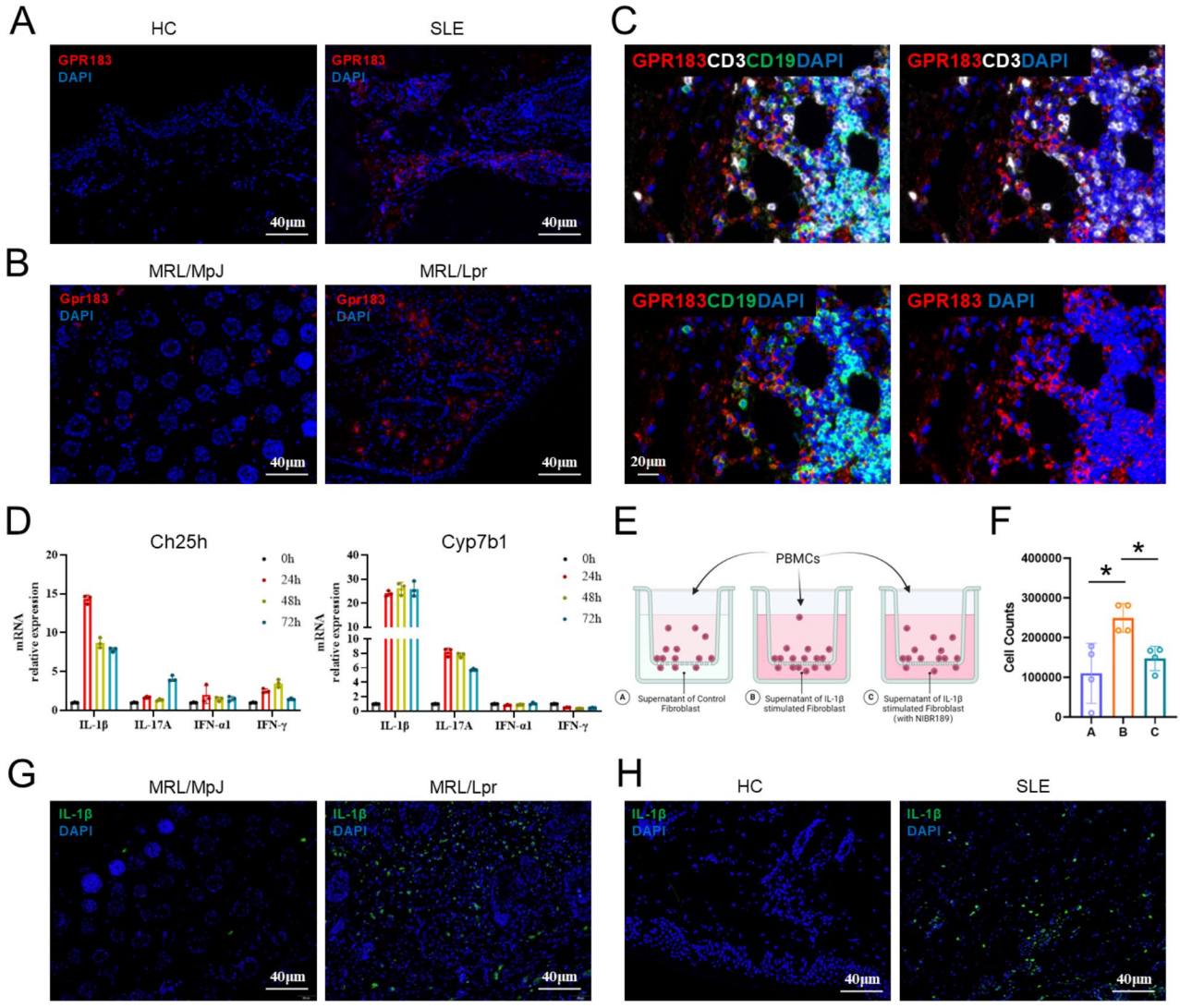


Fig. 4 Increased GPR183^{+} immune cells in lupus skin lesions and their recruitment by IL-1β-stimulated fibroblasts. (**A**) Representative immunohistochemistry images of GPR183 in HC (left) and SLE skin lesions (right) (n = 3). (B) Representative immunohistochemistry images of Gpr183 in MRL/MpJ (left) and MRL/Lpr (right) mice skin (n = 3). (**C**) Representative immunohistochemistry images showed a co-expression of GPR183 and CD3/CD19 in SLE skin lesions. (**D**) RT-qPCR analysis of Ch25h and Cyp7b1 in fibroblasts stimulated with various cytokines (n = 3). (**E**) PBMCs/Fibroblasts conditioned media transwell model. (**F**)Bar graph shows the total number of chemotactic cells in the lower chamber (n = 4). (**G**-**H**) Representative immunohistochemistry images showed an increase in IL-1β in lupus skin lesions (n = 3). The data shown were representatives of three independent experiments. The data are shown as mean ± SEM. The *p* values were calculated using two-way ANOVA test (**D**) or one-way ANOVA analysis (**F**)

Discussion

Our study found that cholesterol oxidation metabolism is abnormal in lupus lesions, with many oxysterols showing abnormal increases. The key genes encoding oxysterols, CH25H and CYP7B1, are also abnormally upregulated in lupus lesions and are mainly expressed by fibroblasts. IL-1β is a key factor mediating the upregulation of CH25H and CYP7B1 in fibroblasts, primarily through the NFκB and p38 MAPK pathways. The upregulation of CH25H and CYP7B1 is crucial for the production of 7α-25-OHC, which plays a role in promoting GPR183^{+} immune cell chemotaxis and can be inhibited by its ligand GPR183 inhibitors. Overall, we revealed that the abnormal metabolism of oxysterols in lupus lesions, particularly in fibroblasts, contributes to immune cell recruitment and may serve as a potential target for therapeutic intervention.

Oxysterols are oxidized products generated during cholesterol metabolism and have been shown to play important roles in various diseases, including colitis, psoriasis, and tumors [11, 22, 23]. Although previous studies have indicated that abnormal cholesterol metabolism contributes to lupus progression [24], the levels of oxysterols in lupus skin lesions were not well understood.

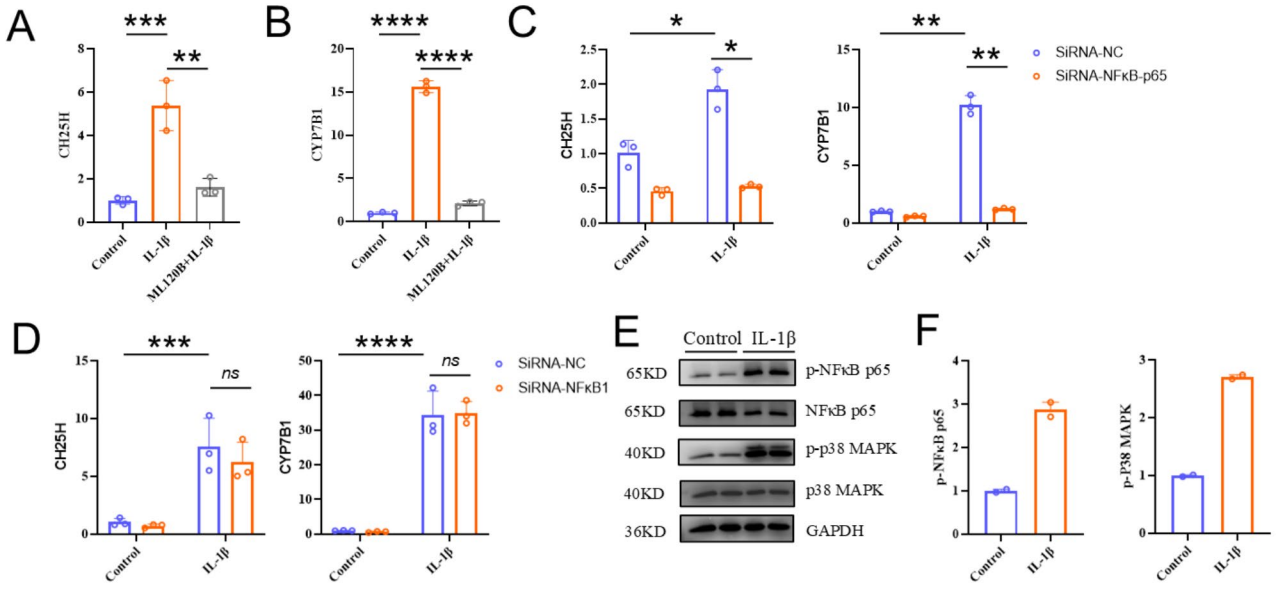


Fig. 5 IL-1β induces expression of CH25H and CYP7B1 in fibroblasts via NFκB and p38 MAPK pathways. (**A**-**B**) RT-qPCR analysis of CH25H (**A**) and CYP7B1 (**B**) in fibroblasts (n = 3). (**C**-**D**) RT-qPCR analysis of CH25H and CYP7B1 in fibroblasts transfected with siRNA-NFκB-p65 (**C**) or siRNA-NFκB1 (**D**), followed by stimulation with control solvent or IL-1β for 24 h (n = 3). (**E**) Western blot analysis of protein expression in fibroblasts treated with control solvent or IL-1β for 0.5 h. (**F**) Quantitative analysis of p-p38 MAPK and p-NFκB-p65 protein expression levels. The data shown were representatives of three independent experiments. The data are shown as mean ± SEM, the *p* values were calculated using one-way ANOVA analysis (**A**-**B**) or two-way ANOVA analysis (**C**-**D**)

We measured the levels of oxysterols in lupus skin lesions using LS/MS and found an upregulation of oxysterols, suggesting their involvement in the development of lupus lesions.

Fibroblasts, as important stromal cells, are known to participate in immune regulation through various mechanisms. In lupus lesions, we further found that fibroblasts express elevated levels of CH25H and CYP7B1, key enzymes for producing 7α-25-OHC, a critical oxysterol. In the colon, stromal cells expressing CH25H and CYP7B1 are involved in constructing lymph nodes, and the absence of these enzymes leads to the loss of lymph nodes and crypt structures [23]. We discovered that fibroblasts can upregulate CH25H and CYP7B1 in response to IL-1β, promoting immune cell recruitment, and this effect is inhibited by GPR183 inhibitors. These findings suggest that fibroblasts can enhance 7α-25-OHC production by upregulating CH25H and CYP7B1, thereby facilitating immune cell recruitment.

To further understand the regulation of CH25H and CYP7B1 in fibroblasts, we conducted pathway inhibition experiments. Our findings demonstrated that both the NFκB and p38 MAPK pathways are critical for the IL-1β-mediated upregulation of these enzymes. Blocking these pathways effectively reduced CH25H and CYP7B1 expression, confirming that IL-1β promotes oxysterol production in fibroblasts through these signaling cascades. Overall, our study identifies fibroblast-derived oxysterols as key contributors to immune cell recruitment in lupus skin lesions. The interplay between IL-1β signaling and ferroptosis-related pathways in fibroblasts not only reveals a novel mechanism of inflammation in lupus but also highlights potential therapeutic targets, such as GPR183, to mitigate immune cell infiltration and inflammation in lupus patients.

Conclusions

Our research reveals abnormal oxysterol metabolism in lupus skin lesions. Fibroblasts upregulate CH25H and CYP7B1 through the IL-1β-mediated NFκB and p38 MAPK signaling pathways. This process promotes immune cell chemotaxis by increasing 7α-25-OHC production. Enhanced PBMCs recruitment by IL-1β-stimulated fibroblasts can be attenuated by a GPR183 inhibitor. These findings not only elucidate a new metabolic mechanism in lupus lesions but also provide a potential therapeutic target for lupus.

Abbreviations

SLE	Systemic lupus erythematosus
LC-MS	Liquid chromatography-mass spectrometry
PBMCs	Peripheral blood mononuclear cells
SPF	Specific pathogen-free
BHT	Butylated hydroxytoluene
T-MAS	Testis-meiosis activating sterol
FF-MAS	Follicular fluid→meiosis→activated→sterol
4b-OH-CHO	4β-hydroxycholesterol
7-OH-CHO	7-Hydroxycholesterol
27-OH-CHO	27-hydroxycholesterol
22-OH-CHO	22-hydroxycholesterol
24-OH-CHO	24-hydroxycholesterol
7 K-25OHCHO	7-keto-25-hydroxycholesterol
7 K-27OH-CHO	7-Keto-27-hydroxycholesterol
6 K-5aOH-CHO	6-keto-5α-hydroxycholesterol

7 K-CHO	7-ketocholesterol
24 S,25-EPOXY-CHO	24 S,25-Epoxycholesterol
5a,6a-EPOXY-CHO	5α,6α-Epoxycholesterol
5b,6b-EPOXY-CHO	5β,6β-Epoxycholesterol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-024-03414-6.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements
Schematic figures were created using https://BioRender.com.

Author contributions
XYC performed study concept and design and performed most experiments. LLOY, contributed to some of experiments; MZ and SJJ provided crucial advice, conceived the studies, interpreted the data, supervised the studies, and revised the manuscript. All authors read and approved the final paper.

Funding
This work was supported by the National Key R&D Program of China (2022YFC3601800), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2022-RC310-04), CAMS Innovation Fund for Medical Sciences (CIFMS, 2021-I2M-1-059), and the National Natural Science Foundation of China (No. 82030097, No.82473535, and No. 32141004).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Human skin biopsies were obtained from the Second Xiangya Hospital of Central South University. Approval was obtained from the ethics committee of Second Xiangya Hospital of Central South University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Dermatology, Hunan Key Laboratory of Medical Epigenomics, Second Xiangya Hospital, Central South University, Changsha 410011, China
[2]Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing 210042, China
[3]Key Laboratory of Basic and Translational Research on Immune-Mediated Skin Diseases, Chinese Academy of Medical Sciences, Nanjing, China
[4]Department of Pathology, Xiangya Hospital, Central South University, Changsha, China

Received: 27 July 2024 / Accepted: 10 October 2024
Published online: 22 October 2024

References

1. Deng GM, Tsokos GC. Pathogenesis and targeted treatment of skin injury in SLE. Nat Rev Rheumatol. 2015;11:663–9.
2. M QLHWWL. Z, V C, L L, A comprehensive review of immune-mediated dermatopathology in systemic lupus erythematosus. J Autoimmun. 2018 Sep;93:1–15.
3. Chen X, Wu Y, Jia S, Zhao M. Fibroblast: a Novel Target for Autoimmune and inflammatory skin diseases therapeutics. Clin Rev Allerg Immu. 2024 Jun;66(3):274–293.
4. Xu Z, Chen D, Hu Y, Jiang K, Huang H, Du Y, et al. Anatomically distinct fibroblast subsets determine skin autoimmune patterns. Nature. 2022;601:118–24.
5. Cavagnero KJ, Li F, Dokoshi T, Nakatsuji T, O'Neill AM, Aguilera C, et al. CXCL12 + dermal fibroblasts promote neutrophil recruitment and host defense by recognition of IL-17. J Exp Med. 2024;221:e20231425.
6. Yi T, Wang X, Kelly LM, An J, Xu Y, Sailer AW et al. Oxysterol gradient generation by lymphoid stromal cells guides activated B cell movement during humoral responses. Immunity. 2012;37:535–48.
7. Chalmin F, Rochemont V, Lippens C, Clottu A, Sailer AW, Merkler D, et al. Oxysterols regulate encephalitogenic CD4(+) T cell trafficking during central nervous system autoimmunity. J Autoimmun. 2015;56:45–55.
8. Liu C, Yang XV, Wu J, Kuei C, Mani NS, Zhang L et al. Oxysterols direct B-cell migration through EBI2. Nature2011;475:519–23.
9. Zeng Q, Wang S, Li M, Wang S, Guo C, Ruan X, et al. Spleen fibroblastic reticular cell-derived acetylcholine promotes lipid metabolism to drive autoreactive B cell responses. Cell Metab. 2023;35:837–e8548.
10. Zhang Y, Gui M, Wang Y, Mani N, Chaudhuri S, Gao B, et al. Inositol-requiring enzyme 1α-Mediated synthesis of Monounsaturated fatty acids as a driver of B cell differentiation and lupus-like Autoimmune Disease. Arthritis Rheumatol. 2021;73:2314–26.
11. Frascoli M, Ferraj E, Miu B, Malin J, Spidale NA, Cowan J et al. Skin γδ T cell inflammatory responses are hardwired in the thymus by oxysterol sensing via GPR183 and calibrated by dietary cholesterol. Immunity 2023;S1074761323000377.
12. Wyss A, Raselli T, Perkins N, Ruiz F, Schmelczer G, Klinke G, et al. The EBI2-oxysterol axis promotes the development of intestinal lymphoid structures and colitis. Mucosal Immunol. 2019;12:733–45.
13. Li J, Lu E, Yi T, Cyster JG. EBI2 augments tfh cell fate by promoting interaction with IL-2-quenching dendritic cells. Nature. 2016;533:110–4.
14. Zheng M, Hu Z, Mei X, Ouyang L, Song Y, Zhou W, et al. Single-cell sequencing shows cellular heterogeneity of cutaneous lesions in lupus erythematosus. Nat Commun. 2022;13:7489.
15. Wu T, Ye L, Wang S, Huang J, Zhang J. Association of lipid lowering drugs and the risk of systemic lupus erythematosus: a drug target mendelian randomization. Front Pharmacol. 2023;14:1258018.
16. Urbain F, Ponnaiah M, Ichou F, Lhomme M, Materne C, Galier S, et al. Impaired metabolism predicts coronary artery calcification in women with systemic lupus erythematosus. Ebiomedicine. 2023;96:104802.
17. Choi WS, Lee G, Song WH, Koh JT, Yang J, Kwak JS, et al. The CH25H-CYP7B1-RORα axis of cholesterol metabolism regulates osteoarthritis. Nature. 2019;566:254–8.
18. Cordier-Dirikoc S, Pedretti N, Garnier J, Clarhaut-Charreau S, Ryffel B, Morel F, et al. Dermal fibroblasts are the key sensors of aseptic skin inflammation through interleukin 1 release by lesioned keratinocytes. Front Immunol. 2022;13:984045.
19. Shi Z, Zhang YP, Hong D, Qiu X, Zheng L, Bian L, et al. Anti-galectin-3 antibodies induce skin vascular inflammation via promoting local production of IL-1β in systemic lupus erythematosus. Int Immunopharmacol. 2022;112:109197.
20. Winkler A, Sun W, De S, Jiao A, Sharif MN, Symanowicz PT, et al. The Interleukin-1 receptor-Associated kinase 4 inhibitor PF-06650833 blocks inflammation in Preclinical models of Rheumatic Disease and in humans enrolled in a Randomized Clinical Trial. Arthritis Rheumatol. 2021;73:2206–18.
21. Biffi G, Oni TE, Spielman B, Hao Y, Elyada E, Park Y, et al. IL1-Induced JAK/STAT signaling is antagonized by TGFβ to shape CAF heterogeneity in pancreatic ductal adenocarcinoma. Cancer Discov. 2019;9:282–301.
22. Foo CX, Bartlett S, Chew KY, Ngo MD, Bielefeldt-Ohmann H, Arachchige BJ et al. GPR183 antagonism reduces macrophage infiltration in influenza and SARS-CoV-2 infection. Eur Respir J. 2023 Mar 9;61(3):2201306.
23. Emgård J, Kammoun H, García-Cassani B, Chesné J, Parigi SM, Jacob JM, et al. Oxysterol sensing through the receptor GPR183 promotes the lymphoid-tissue-inducing function of innate lymphoid cells and colonic inflammation. Immunity. 2018;48:120–e1328.

24. Zhao M, Mei Y, Zhao Z, Cao P, Xin Y, Guo Y et al. Abnormal lower expression of GPR183 in peripheral blood T and B cell subsets of systemic lupus erythematosus patients. Autoimmunity. 2022;55:429–42.

Publisher's note