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Integrated analysis of dermatomyositis reveals heterogeneous immune infiltration and interstitial lung disease-associated endotype

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Abstract

Background Dermatomyositis (DM) is an autoimmune disease with a high rate of disability and mortality especially in DM with concurrent interstitial lung disease (DM-ILD). Little is known about inflammatory signature and heterogeneous endotypes of DM.

Objective We aimed to illustrate the systemic inflammatory signature of DM and define an ILD-associated endotype.

Methods Olink proteomic analysis was performed on serum samples obtained from DM patients ($n=32$), DM patients with ILD ($n=16$), and healthy controls ($n=19$). Transcriptomic data from skin samples was utilized to assess immune infiltration and investigate the correlation between protein and mRNA levels of biomarkers. Additionally, the prognostic value and clinical significance of identified biomarkers were validated through follow-up studies of DM patients and immunofluorescence analysis of skin tissues.

Results Proteomic data revealed the inflammatory signature of DM, with GO and KEGG enrichment analyses identifying chemotaxis-related pathways. Transcriptomic analysis of skin samples indicated upregulated inflammatory responses and M1 macrophage infiltration in DM. Two chemokines, CXCL10 and CXCL11, were identified as highly associated with immune infiltration and DM progression.

Conclusions Our data suggest that serum CXCL10 and CXCL11 reflect the inflammatory burden of DM. The identified biomarkers hold promise for determining an ILD-associated endotype and predicting clinical outcomes, thereby paving the way for timely management of DM and prevention of complications.

Key messages

• Integrated analysis of serum proteomics and skin biopsy transcriptomics identified key analytes present in both protein and RNA transcripts that correlate with the degree of skin involvement in DM and the onset of ILD.

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• CXCL10 and CXCL11 were confirmed to reflect the local immune environment of the skin and hold the potential to assess ILD risk.

• An ILD-associated endotype in DM was characterized by distinct inflammatory profiling and heterogeneous features, paving the way for early DM-ILD diagnoses and improved clinical management.

Keywords Dermatomyositis, Interstitial lung disease, Proteomic, Immune infiltration, Endotype

Introduction

Dermatomyositis (DM) is an idiopathic immune-mediated disorder, characterized by diverse cutaneous manifestations and muscle inflammation [1]. The diagnosis and treatment of DM pose significant challenges. Beyond the evident skin rash and myositis, DM frequently involve systemic complications, including interstitial lung disease (ILD) and malignancy [2]. Systemic involvement amplifies the complexity of the disease, rendering it more intractable and contributing to increased mortality and disability rates. Despite extensive research, the precise pathogenesis of DM remains elusive, with potential links to genetics, environment, and immunity [1, 3]. Notably, studies have spotlighted the involvement of various immune cells such as T cells, B cells, macrophages, dendritic cells, and their secreted cytokines and chemokines in the occurrence and development of this heterogeneous disease [4, 5]. We propose that dermatomyositis (DM) can be stratified into prognostically relevant endotypes characterized by distinct features such as inflammation or immune infiltration, and endotype-specific therapies that target these features should be considered.

Interstitial lung disease (ILD), a common and often severe complication in up to approximately 40% of DM cases, stands out as a major contributor to patient mortality, characterized by clinical manifestations such as cough, post-activity shortness of breath, and dyspnea [6, 7]. High-resolution computed tomography (HRCT) for comprehensive chest scanning and pulmonary function testing (PFT) (including carbon monoxide diffusion function) for assessing ILD severity, serve as available tools for diagnosis and follow-up [8]. The challenge lies in the lack of a clear correlation between the severity of skin or muscle disease and ILD, potentially delaying timely identification and treatment initiation. Hence, early identification of ILD becomes imperative for improvement of prognosis. Regrettably, the current state of risk assessment for DM-ILD remains insufficient. Although recommended diagnostic procedures include HRCT and PFT, irreversible lung changes may have already occurred by the time of detection. Recent research has illuminated potential risk factors for DM combined with ILD, including positive anti-melanoma differentiation-associated gene 5 antibodies, clinically amyopathic dermatomyositis (CADM), and seborrheic dermatitis-distributed rash [9–12]. The melanoma differentiation-associated gene 5 (MDA5) antibody is strongly associated with interstitial lung disease (ILD), including rapidly progressive ILD, and has high specificity. Most patients who are anti-MDA5 positive exhibit lung involvement. However, the positive rate for anti-MDA5 antibodies is relatively low (approximately 10–30%), and some ILD patients do not test positive for this antibody [13]. While these risk factors offer valuable insights into the development of ILD in DM patients, concerns regard their accuracy and sensitivity. Thus, there is an emergent need for further exploration into refined risk assessment strategies.

The pivotal role of autoimmunity in the etiology of DM and ILD is increasingly recognized [14]. Both diseases manifest as inflammatory disorders, and prevailing beliefs link serum inflammatory cytokines to their pathogenesis. [15] Cytokines, serving as essential signaling molecules, coordinate inflammatory responses, which are produced by diverse cells, including immune cells, endothelial cells, and epithelial cells. [16] A host of cytokines, including C-X-C Motif Chemokine Ligand (CXCL) 10, interleukin (IL)−18, IL-15, IL-6, IL-23, IL-27, IL-35, tumor necrosis factor (TNF)-α, and IL-8, have been implicated in the pathogenesis of DM or DM-ILD [4, 5, 17]. Elevated levels of these cytokines in serum or expression in skin and muscle tissue have been noted in DM patients. However, the role of circulating blood systemic inflammatory mediators in the pathogenesis of DM-ILD remains inadequately understood.

To address this knowledge gap, we have initiated a proteomic analysis, employing high-efficiency assays to characterize systemic inflammatory blood signature of DM. Our innovative approach seeks to validate the hypothesis of proteomic features in the presence of ILD and explore potential risk factors for ILD in DM patients.

Methods

Cohort of study

We conducted a retrospective cohort study at Zhongshan Hospital (Shanghai, China), spanning the years 2016 to 2021. The study included consecutive patients with active, early (< 12 months disease duration) DM and clinically amyopathic DM (CADM), naïve to steroids and immunosuppressive therapy, along with healthy controls (HC). DM/CADM diagnoses were based on

either Bohan and Peter's criteria or the 2017 EULAR/ACR classification criteria [18, 19]. The diagnosis of ILD was established by respiratory physicians using respiratory symptoms, HRCT, and PFT, adhering to the 2022 ATS/ERS/JRS/ALAT guideline [20]. Every DM patient was asked to undergo HRCT and PFT assessments every three months during the first year of follow-up. Patients were instructed to report any respiratory symptoms immediately, in which case HRCT and PFT were performed promptly to reassess ILD status. Exclusion criteria comprised juvenile DM (diagnosis at < 18 years), other autoimmune diseases or active inflammatory diseases, uncontrolled systemic conditions, and current systemic immunosuppressive therapy. Clinical data, including demographics, clinical presentation, physical examination results, and comorbidities, were collected at diagnosis and during follow-up.

Blood samples and proteomic analysis

Blood samples were collected at the time of diagnosis, ensuring the absence of targeted drug use and active DM. Serum, isolated from whole blood, was stored at −80 °C until analysis. The Olink Proseek® multiplex assay, specifically the pre-designed Inflammation panel with 92 protein biomarkers, was employed for proteomic analysis [21]. The Olink platform provided normalized protein expression (NPX) values reported on a log2 scale, where higher NPX values indicated elevated protein concentrations without providing absolute concentration measurements.

Transcriptomic analysis of skin tissues

Gene expression matrix of skin and muscle tissues from DM and HC were downloaded from NCBI-GEO (GSE46239 and GSE143323). Gene set enrichment analysis (GSEA) was performed using software provided by the Broad Institute. Immune cell proportion of each skin sample was obtained by the "CIBERSORT" R package.

Immunofluorescence staining

For histological analysis, skin tissues were fixed in 4% formaldehyde for paraffin embedding and then mounted on slides. H&E staining and immunofluorescence staining were conducted to evaluate macrophages infiltration and inflammatory response of samples. Primary antibodies were listed as follows: anti-CXCL10 (10,937–1-AP, ProteinTech), anti-CXCL11 (10,707–1-AP, ProteinTech). Quantification of the staining was conducted using ImageJ software.

Statistical analysis

Quality control of Olink proteomic results was conducted, and standard two-tailed t tests were employed to compare DM patients with or without ILD to HC using log2-transformed data. Biomarkers were considered differentially expressed if the fold change (FC) was > 1.2 and the P value was < 0.05. R (4.1.3) were used for data processing and statistical analysis. Wilcoxon test was performed to evaluate the differentially expression of immune cells in skin specimens. Spearman correlation analysis was conducted to assess the correlations between CXCL10/11 expression and immune infiltration of samples.

Results

Upregulated inflammation and M1 macrophage infiltration in DM

Considering that DM involves the muscles and skin, we utilized skin and muscle tissues RNA-seq data of DM and HC from NCBI-GEO to investigate the correlation between DM proteomic and transcriptomic gene markers. Gene Set Enrichment Analysis (GSEA) revealed significant enrichment of inflammation response pathway and the interferon gamma pathway in DM skin tissues compared to controls, further validating the inflammatory signature of DM (Fig. 1a). Immune cell presence in the skin, as estimated by CIBERSORT, reflects proportions derived from gene expression signatures rather than absolute cell counts. These proportions revealed a significant enrichment of M1 macrophages in DM skin samples compared to controls. Furthermore, immune cell infiltration analysis demonstrated a marked upregulation of the M1 macrophage ratio in DM skin tissues relative to HC, emphasizing the critical involvement of macrophages in the development and progression of DM (Fig. 1b). Building on these findings, we hypothesized that cytokines might play a central role in this macrophage-driven inflammation, which led us to conduct proteomic studies comparing serum samples from DM patients and HC to identify potential key mediators.

Demographic and clinical characteristics of the study population

Forty-eight patients with DM and 19 HC were enrolled. Among the DM patients, 16 were complicated by ILD. The demographics and clinical features of participants are presented in Table 1. The three groups (DM, DM-ILD, HC) exhibited similar distributions of age at onset (56.16 ± 10.98 y vs 58.25 ± 12.81 y vs 55.44 ± 8.053 y) and race. Notably, DM patients with ILD demonstrated a higher prevalence of males (44% vs 19%), clinically amyopathic dermatomyositis (CADM) (12% vs 3%), inverse Gottron papules (44% vs 16%), vasculitis (19% vs 3%), mechanic's hands (19% vs 6%), seborrheic dermatitis-distributed rash (50% vs 9%), and positive anti-MDA5 antibodies (44% vs 0%) compared to patients without ILD.

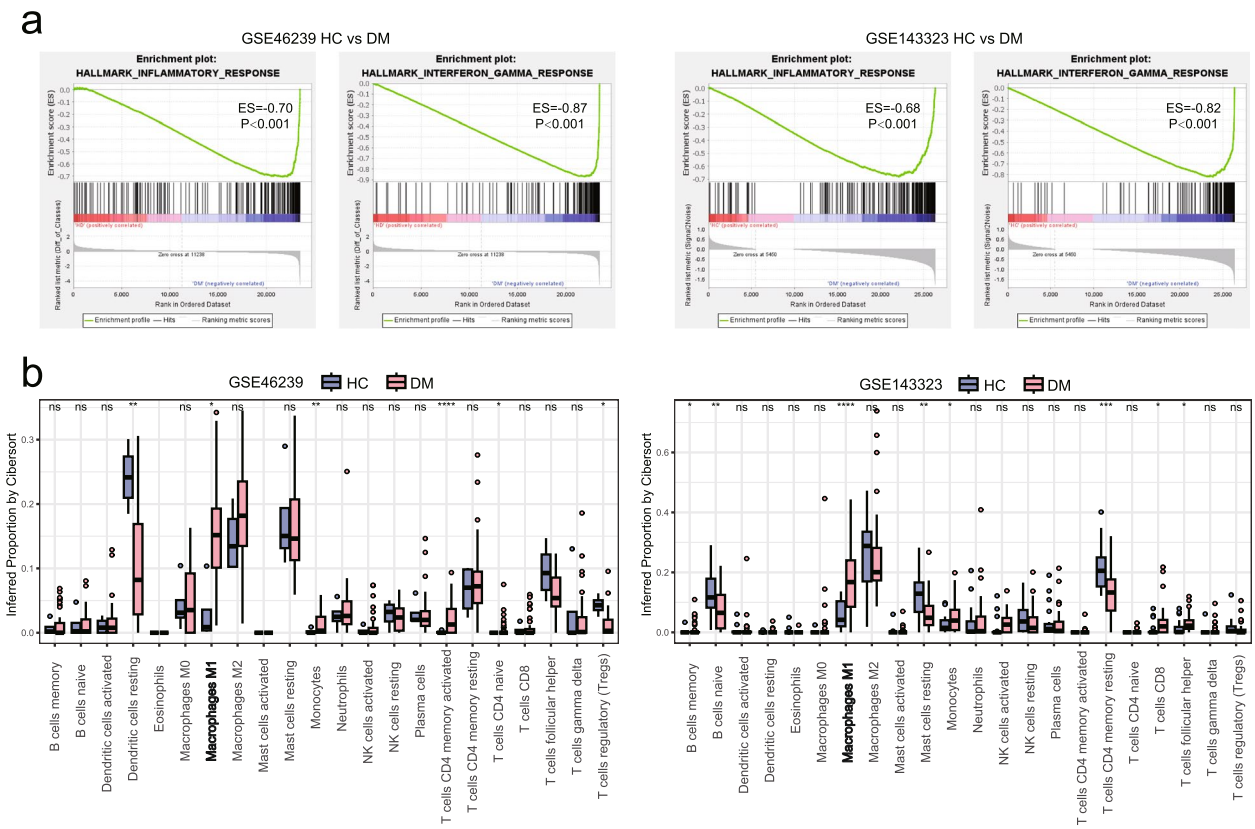

Fig. 1 Heightened inflammation and M1 macrophage infiltration in DM. **a** GSEA results of GSE46239 and GSE143323 depict enrichment of the interferon gamma and inflammatory response pathway in DM group compared to HC. **b** Expression of immune cells in DM group compared to HC. DM, dermatomyositis; HC, healthy controls

Proteomic analysis of inflammatory biomarkers among DM, DM-ILD and HC

Utilizing a 92-protein biomarker Olink panel, we conducted a comprehensive analysis involving DM, DM-ILD patients and HC. The heatmap illustrated the profiles of inflammatory proteins among the three groups (Fig. 2). Employing a criterion of FC > 1.2 and p-value < 0.05, differentially expressed proteins (DEPs) between indicated groups were presented through volcano plots (Fig. 3a). The gene ontology (GO) analysis indicates that DEPs are primarily concentrated in pathways related to cytokine and chemokine (Fig. 3b). Similarly, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis reveals that DEPs are mainly enriched in cytokine–cytokine receptor interaction pathway (Fig. 3c).

CXCL10/11 expression positively correlated with M1 macrophage infiltration in DM

Subsequently, we specifically analyzed 92 inflammatory markers overlapping with Olink measurements. Our findings unveiled a significant correlation between protein and mRNA differences in DM compared to healthy tissue biopsies (Fig. 4a). Importantly, genes exhibiting increased mRNA expression often displayed a concordant rise in protein levels, indicating a close relationship between systemic inflammation and local lesions in DM. Integrating the proteomic results with two GEO datasets, cytokines such as CXCL10 and CXCL11 were found to be significantly upregulated in both blood and skin, suggesting their potential role in DM. To further elucidate the key genes implicated in DM progression, we conducted a differential expression analysis of two datasets. Four intersections of Differentially Expressed Proteins (DEPs) and Differentially Expressed Genes (DEGs) were further investigated using a Venn diagram (Fig. 4b). Consistently, CXCL10 and CXCL11 emerged as hub genes, exhibiting upregulation in both peripheral blood and skin lesions. Subsequently, we employed Receiver Operating Characteristic (ROC) tests to validate the diagnostic power of CXCL10 and CXCL11 across two GEO datasets (Fig. 4c). Given the heightened inflammatory microenvironment in DM skin tissues, we sought to explore the relationship between these hub genes and the M1 macrophage ratio. Spearman tests revealed a significant correlation between the expression levels of CXCL10 and CXCL11 and the M1 macrophage ratio in both datasets,

Table 1 Baseline demographics of DM, DM-ILD patients and HC

	Dermatomyositis Comorbid interstitial lung disease		Healthy Controls (*N* = 19)
	No (*N* = 32)	Yes (*N* = 16)	
Demographics			
Gender, female	26 (81%)	9 (56%)	14 (74%)
Age, mean (SD)	56.16 ± 10.98 y	58.25 ± 12.81 y	55.44 ± 8.053 y
Race, Asian	32 (100%)	16 (100%)	19 (100%)
Dermatomyositis phenotype			
Classic (CDM)	31 (97%)	14 (88%)	N/A
Clinically amyopathic (CADM)	1 (3%)	2 (12%)	N/A
Rash			
Heliotrope rash	22 (69%)	8 (50%)	N/A
Gottron papules	16 (50%)	9 (56%)	N/A
Inverse Gottron papules	5 (16%)	7 (44%)	N/A
Gottron sign	15 (47%)	8 (50%)	N/A
V sign	16 (50%)	7 (44%)	N/A
Shawl sign	13 (41%)	6 (38%)	N/A
Nail fold changes	24 (75%)	13 (81%)	N/A
Poikiloderma	25 (78%)	10 (63%)	N/A
Vasculitis	1 (3%)	3 (19%)	N/A
Mechanic's hands	2 (6%)	3 (19%)	N/A
Seborrheic dermatitis-distributed rash	3 (9%)	8 (50%)	N/A
Myositis specific antibodies			
Anti-MDA-5 antibodies	0 (0%)	7 (44%)	N/A
Anti-TIF1γ antibodies	8 (25%)	0 (0%)	N/A
Other clinical features			
With cancer	5 (16%)	0 (0%)	N/A
RP-ILD	N/A	4 (25%)	N/A

DM Dermatomyositis, *ILD* Interstitial lung disease, *HC* Healthy controls, *MDA-5* Melanoma differentiation-associated gene 5, *TIF1γ* Transcriptional intermediary factor 1γ, *RP-ILD* Rapidly progressive ILD

underscoring the pivotal role of these chemokines in DM skin lesions (Fig. 4d). Stratifying the DM samples based on the expression of CXCL10 and CXCL11 into low and high expression groups, we observed a noteworthy upregulation in the high expression group compared to the low expression group (Fig. 4e).

An ILD-associated cluster was identified within DM population

To further explore the correlation between CXCL10/11 and disease activity as well as organ involvement, we divided the DM cohort into two clusters based on the expression levels of CXCL10 and CXCL11. The demographic and clinical features of patients in 2 DM clusters are presented in Supplementary Table 1. Hematoxylin and eosin (H&E) staining, along with immunofluorescence staining, were utilized to assess the immune status of skin tissues in the two DM clusters ($n = 3$). Consistent with the results of immune infiltration analysis, immunofluorescence staining images of DM cluster 2 revealed a higher presence of CXCL10/11 + cells and CD86 + M1 macrophages (Fig. 5a and b), suggesting enhanced chemotaxis of immune cells and an exacerbated inflammatory microenvironment in skin lesions. The specific expression levels of CXCL10 and CXCL11 across the four groups were illustrated by violin plots (Fig. 5c), indicating markedly higher expression levels of CXCL10/11 in DM cluster 2, akin to DM-ILD. Additionally, the overall inflammatory profiles of the two DM clusters indicated significant heterogeneity in DM (Supplementary Fig. 1), suggesting differed disease activity and prognoses. In addition to CXCL10 and CXCL11, the differential expression of MCPs and TNF-α suggests their potential involvement in the development and progression of DM. These proteins, primarily associated with the Th1 immune and chemotactic axis, highlight the pivotal role of chemokine-mediated positive feedback loops in DM progression. MCPs are well-recognized profibrotic chemokines implicated in ILD and are markers of innate immunity that stimulate the chemotaxis of monocytes and dendritic cells toward inflammatory sites [22]. Follow-up of

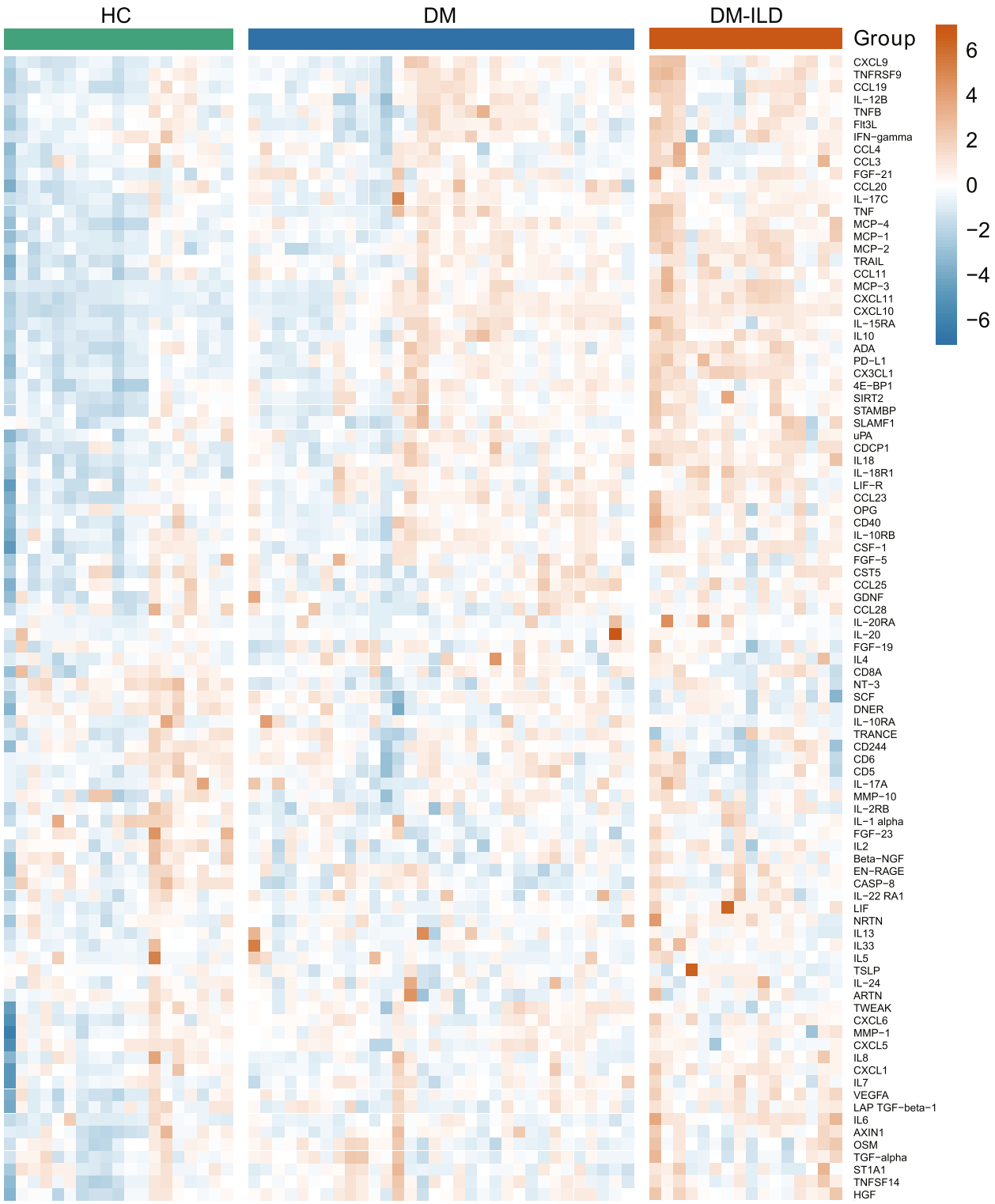

Fig. 2 Comprehensive inflammatory signature of DM. Heatmap illustrating the profile of inflammatory proteins among DM, DM-ILD and HC groups. DM, dermatomyositis; ILD: interstitial lung disease; HC, healthy controls

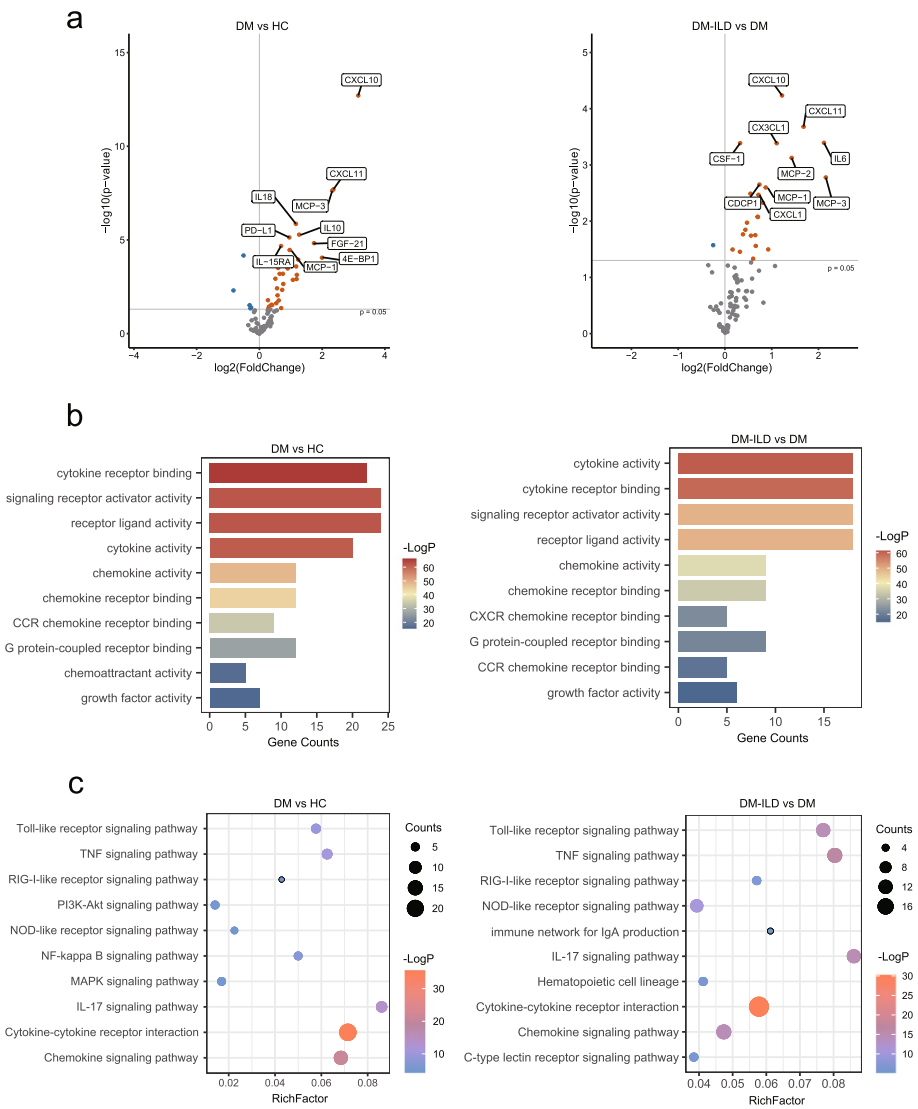

Fig. 3 Enrichment Analysis of differentially expressed proteins. **a** Volcano plots illustrating the significant differentially expressed proteins between the indicated groups. Red and blue dots represent upregulated and downregulated proteins with a *p*-value < 0.05, respectively. Grey dots represent proteins with a *p*-value > 0.05. The top ten significant proteins are labeled with corresponding gene symbols. **b** Top ten pathways in GO molecular function enrichment analysis of DEPs between indicated groups. **c** Top ten pathways in KEGG enrichment analysis of DEPs between indicated groups. DM, dermatomyositis; ILD: interstitial lung disease; HC, healthy controls

the two DM clusters revealed divergent probabilities of ILD onset. In cluster 1, only two patients developed ILD (2/16, 12%) in one year. In contrast, cluster 2 demonstrated a higher incidence of ILD (7/16, 44%). These findings underscore the potential predictive value of the identified biomarkers in determining ILD onset in DM patients.

Discussion

ILD is a prevalent complication in DM patients, often contributing to a poorer prognosis [23, 24]. Timely diagnosis and identification of associated complications such as ILD are critical for improving prognosis outcomes of DM patients [25]. However, the intricate pathogenesis of DM and its associated ILD remains elusive, with potential mechanisms involving cellular immunity, cytokine pathways, and genetic susceptibility. Although certain phenotypes such as muscle involvement, autoantibodies and rash have been implicated in predicting ILD, their accuracy and efficiency are limited [1, 9]. Positive anti-MDA5 antibodies are highly indicative of interstitial lung disease (ILD) in patients with DM and serve as a valuable early clinical warning. When combined with specific rashes, such as seborrheic dermatitis-distributed rash, as noted in our previous study, we can more accurately

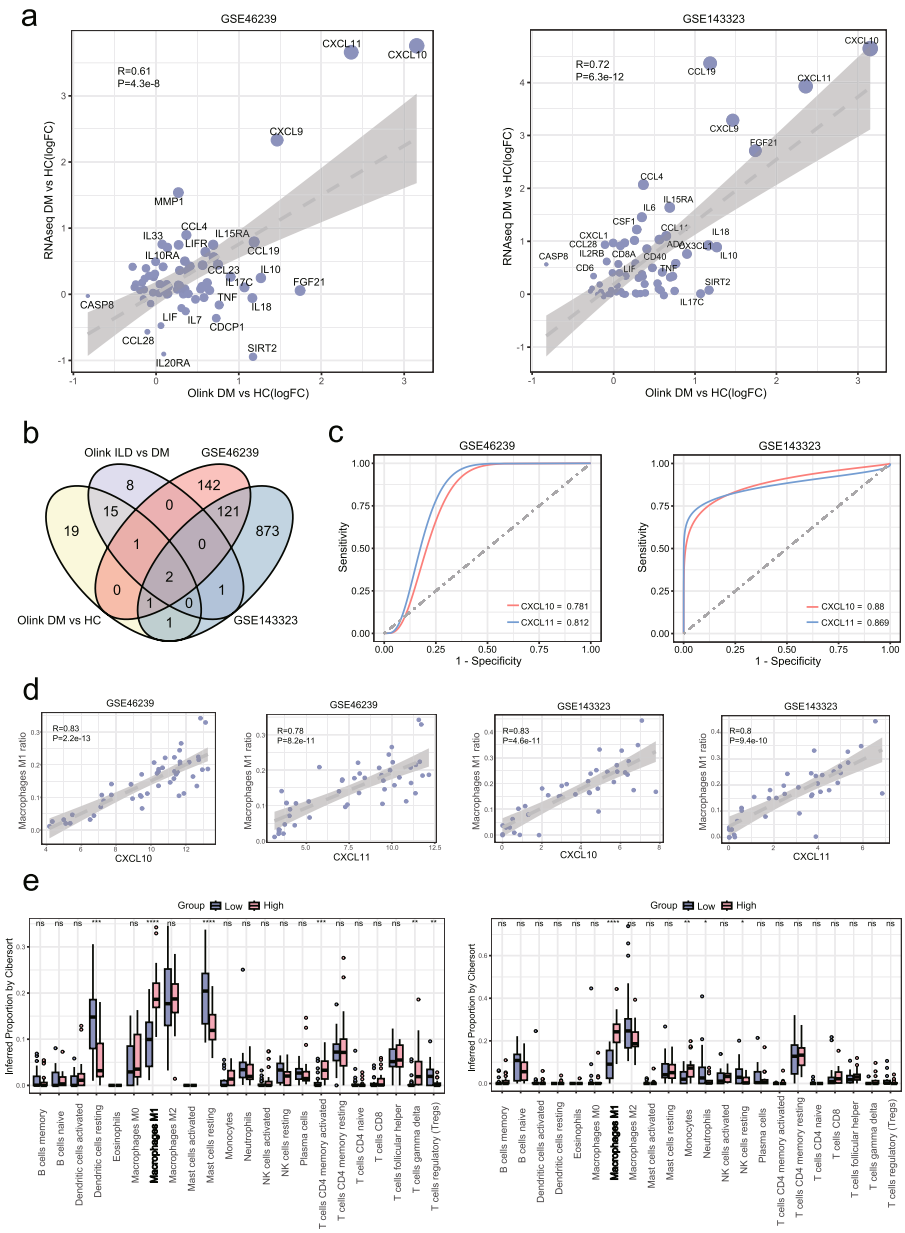

Fig. 4 Close relation between CXCL10/11 expression and M1 macrophage infiltration in DM. **a** Spearman's correlation scatterplots illustrate the log2FoldChange of 92 inflammatory genes in skin tissues of DM patients compared with normal skin (y-axis) versus the log2FoldChange proteomic differences in DM patients compared with controls (x-axis). The size of the circles represents the absolute difference (in log2FC) between protein or gene expressions of DM versus HC. **b** Venn diagram shows differentially expressed proteins and genes among the indicated groups. **c** Receiver operating characteristics (ROC) curves generated for CXCL10 and CXCL11 to assess area-under-the-curve (AUC), sensitivity, and specificity metrics in discerning DM from HC. **d** The expression level of CXCL10/11 was correlated with the M1 macrophage ratio of skin samples in two datasets. Correlation was measured using Pearson correlation coefficient. **e** Expression of immune cells in DM patients with high and low expression of CXCL10 and CXCL11. DM, dermatomyositis; HC, healthy controls

predict the likelihood of ILD in these patients [12]. However, the positive rate of anti-MDA5 antibodies in DM is not sufficiently high, and the incidence of these specific rashes is relatively low. Therefore, our team aims to identify additional biomarkers with greater sensitivity and broader applicability, in hopes of improving early clinical assessment of ILD risk in DM. Consequently, there is a crucial need for novel, sensitive, and synergistic biomarkers to identify DM patients and predict ILD risk for enabling early interventions.

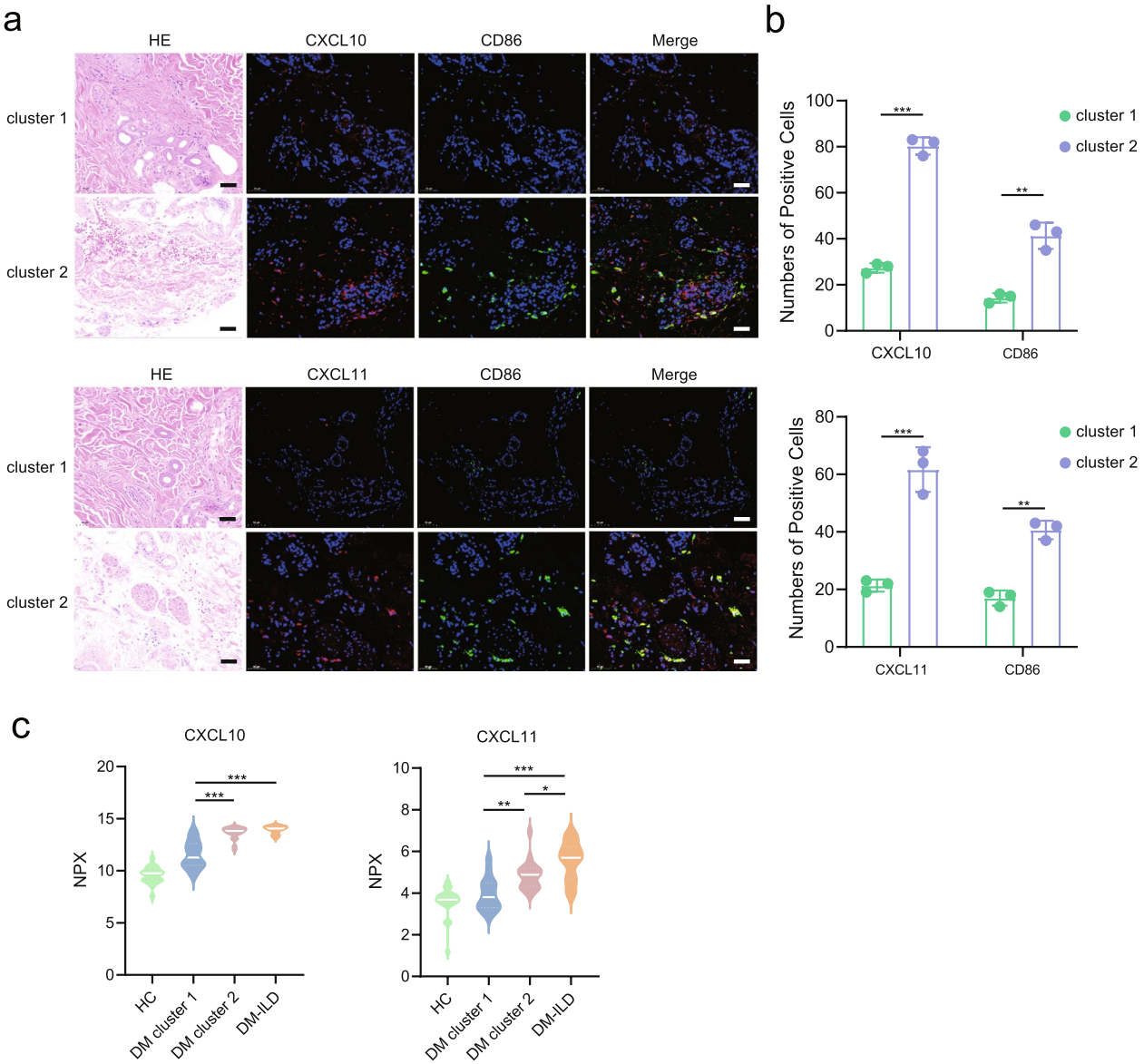

Fig. 5 Prognostic value of identified biomarkers. **a** Histological examinations of skin tissues for measuring CXCL10/11 and CD86. Scale bar: 100 μm. **b** Quantitative expression levels of CXCL10/11 and CD86 positive cells ($n = 3$). The bar graphs represent mean ± SD; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. **c** Violin plots displaying the expression levels of CXCL10 and CXCL11 in HC, DM cluster 1, DM cluster 2, and DM-ILD. The median is presented as a white line. DM, dermatomyositis; ILD: interstitial lung disease; HC, healthy controls. NPX, normalized protein expression

In this cohort, based on the clinical information of patients, we found that possible risk factors for DM combined with ILD include male, CADM, anti-MDA5 antibodies, inverse Gottron papules, vasculitis, mechanical's hands, seborrheic dermatitis-distributed rash, aligning with previous reports [9, 11, 12, 26]. Additionally, analysis of demographic and clinical characteristics sheds light on the heterogeneity of DM and its association with ILD. The balanced age and race distribution across DM, DM-ILD and HC groups suggest a well-matched study cohort for robust comparisons.

Proteomic analyses of serum samples have provided valuable insights into systemic inflammatory processes in DM. Our cohort, comprising 48 DM patients (including 16 with ILD) and 19 HC, provided a robust foundation for investigating the intricate relationship between inflammatory markers and clinical outcomes. Using the

Olink Proteomic technology's Target 96 Inflammation Panel, specifically chosen for its ability to conduct large-scale multiplex assays and analyses, our research unveiled distinct inflammatory profiles of DM and DM-ILD compared to HC. The upregulated expression of cytokines underscores the systemic inflammatory nature of DM, reinforcing existing literature on immune dysregulation in DM pathogenesis. Moreover, the upregulation of CXCL10 and CXCL11 in both proteomic and transcriptomic data, suggested a potential link between systemic inflammation and local lesions in DM.

To further exploit the correlation between CXCL10/11 and DM, we investigated the immune cell proportion in DM skin tissues and found the M1 macrophage ratio is significantly upregulated in DM compared to HC. More importantly, the expression level of CXCL10/11 is positively correlated with M1 macrophage ratio, and this hypothesis was further confirmed by immunofluorescence staining of skin tissues of DM and HC. Two distinct groups (Cluster 1 and Cluster 2) were divided by expression of CXCL10/11 in DM patients without ILD. Cluster 1, displaying profiles akin to HC, suggested limited inflammation and a favourable prognosis. Cluster 2, characterized by heightened inflammation, exhibited similarities with DM-ILD, indicating a potential pre-ILD condition may require early intervention. These results emphasize the predictive value of CXCL10/11 in determining ILD risk.

The identified biomarkers, CXCL10 and CXCL11, predominantly associated with the Th1 immune and chemotactic axis, underscore the pivotal role of chemokine-mediated positive feedback loops in the progression of DM. Kameda's study revealed significantly elevated serum levels of CXCL10 and CXCL11 in autoimmune diseases with ILD [27]. Notably, CXCL10 has been recognized as a useful biomarker for assessing cutaneous disease activity in patients with DM and CADM [5]. The underlying mechanism of ILD can be summarized as follows: systemic inflammation caused by DM leads to the abnormal activation of monocytes and the mass secretion of chemokines, further resulting in local inflammation of the skin and muscles [28]. Due to the abundance of macrophages in the lungs, activated monocytes from the bloodstream enter the lungs and differentiate into M1 macrophages. These activated M1 macrophages secrete elevated levels of inflammatory factor like TNF, exacerbating the Th1 cascade response and collectively forming an inflammatory factor storm, thereby accelerates the progression of lung inflammation in DM-associated ILD [29].

The advantage of biomarkers derived from blood over many other auxiliary diagnostic means lies in their high efficiency, convenience, and affordability, making them suitable for early diagnosis, prognostic assessment, and follow-up of diseases. The cytokines in serum are closely related to diseases and are emerging useful tools in the field of autoimmune inflammatory diseases. Through our research, these proven cytokines can assist clinicians in diagnosing and predicting the tendency of lung involvement in DM, and will increasingly be used to evaluate response to treatment, predict outcomes, and ultimately help patients choose early and appropriate treatment. While our study provides valuable insights into the inflammatory landscape and underlying mechanisms of DM and DM-ILD, certain limitations should be acknowledged. The modest sample size warrants further validation in larger cohorts, and the retrospective nature of study introduces inherent biases. High-throughput work, such as the proteomic and transcriptomic analyses performed in this study, is often specific to a single time point. While our findings highlight CXCL10 and CXCL11 as potential biomarkers for DM and ILD risk, we recognize that longitudinal studies are necessary to validate their temporal sensitivity and robustness. Future investigations should focus on the dynamic changes of these biomarkers over time to confirm their clinical utility in disease monitoring and management.

This study provides inflammatory proteomic signature of DM, offering valuable insights for early intervention in managing DM patients at risk of developing ILD. The findings hold promise for improving the early diagnosis of ILD in DM patients, enabling timely interventions and therapeutic adjustments.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03494-y.

Supplementary Material 1.

Supplementary Material 2. Supplementary Figure 1: Heatmap presenting the distinctive inflammatory signature of 2 DM clusters.

Supplementary Material 3. Supplementary Figure 2: Heatmap showing the proteomic profiles of DM patients categorized by autoantibodies.

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Not applicable.

Authors' contributions
X.X., T.Q. and K.S. contributed to sample collection and performed the statistical analyses. X.H. and J.H. and X.W. collected clinical information from patients. J.G. contributed to data interpretation and drafted the manuscript. J.Y. designed this project and supported this work. All authors read and approved the final version of the manuscript.

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

Declarations

Ethics approval and consent to participate
Informed consent was obtained from all participants, and the study was approved by the Zhongshan Hospital of Fudan University Institutional Review Board with approval number B2020-410R.

Consent for publication
Not applicable.

Competing interests
The authors declared no competing interests.

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