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Original Article

Multi-omics approach identifies PI3 as a biomarker for disease severity and hyper-keratinization in psoriasis

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ABSTRACT

Background: Psoriasis is an immune-mediated inflammatory skin disease. Psoriasis severity evaluation is important for clinicians in the assessment of disease severity and subsequent clinical decision making. However, no objective biomarker is available for accurately evaluating disease severity in psoriasis.
Objective: To define and compare biomarkers of disease severity and progression in psoriatic skin.
Methods: We performed proteome profiling to study the proteins circulating in the serum from patients with psoriasis, psoriatic arthritis and ankylosing spondylitis, and transcriptome sequencing to investigate the gene expression in skin from the same cohort. We then used machine learning approaches to evaluate different biomarker candidates across several independent cohorts. In order to reveal the cell-type specificity of different biomarkers, we also analyzed a single-cell dataset of skin samples. In-situ staining was applied for the validation of biomarker expression.
Results: We identified that the peptidase inhibitor 3 (PI3) was significantly correlated with the corresponding local skin gene expression, and was associated with disease severity. We applied machine learning methods to confirm that PI3 was an effective psoriasis classifier, Finally, we validated PI3 as psoriasis biomarker using in-situ staining and public datasets. Single-cell data and in-situ staining indicated that PI3 was specifically highly expressed in keratinocytes from psoriatic lesions.
Conclusion: Our results suggest that PI3 may be a psoriasis-specific biomarker for disease severity and hyper-keratinization.

1. Introduction

Psoriasis is a complex skin disease which is caused by persistent inflammatory infiltrates resulting in hyper-keratinization [1]. The histology of skin lesion in psoriasis is characterized by epidermal hyperplasia and dermal infiltration of immune cells. Psoriasis primarily affects the skin; however, it may also affect nails and peripheral and axial joints, which further negatively impacts the quality of life of the patients.

In routine clinical practice, the physicians measure psoriasis severity by measurements such as the psoriasis area and severity index (PASI) [2], body surface area (BSA) [3] and physician's global assessment (PGA) [4]. PASI, BSA, PGA have been used for many decades and their reliability as scores differentiating mild from moderate-to-severe has been validated [5]. However, these measurements are

Abbreviations: ANOVA, analyses of variance; AS, ankylosing spondylitis; ASAS, spondylo-arthritis international society criteria; BH, Benjamini-Hochberg; BSA, body surface area; CASPAR, classification criteria for psoriatic arthritis; CRP, C-reactive protein; DIA-MS, data independent acquisition-mass spectrometry; ESR, erythrocyte sedimentation rate; GEO, gene expression omnibus; GO, gene ontology; LCN2, lipocalin 2; LRT, likelihood ratio test; PASI, psoriasis area severity index; PBMCs, peripheral blood mononuclear cells; PGA, physician's global assessment; PI3, peptidase inhibitor 3; PsA, psoriatic arthritis; PSI, psoriasis severity index; RF, random forest; RFE, recursive feature elimination; SVM, support vector machines

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quite subjective. There is a high inter- and intra-observer variability in the assessment of the various parameters of the measurements [6]. Due to the subjectivity and heterogeneity of these severity measures, objective biomarkers are badly needed to systemically evaluate the disease severity of psoriasis in clinical practice.

High-throughput profiling techniques (omics) have been widely used to explore the biomarkers and molecular mechanisms in psoriasis. Several multi-omics studies with transcriptome and proteome profiles were reported for the biomarkers discovery and molecular mechanisms exploration [7–11]. Some of these studies identified high-confidence differentially expressed genes/proteins (DEGPs) through the transcriptome-proteome integration from same patient cohort [7,9,11]. For instance, Krueger's group reported that psoriasis and hidradenitis suppurativa shared Th1/Th17 signature and upregulation of atherosclerosis-related proteins [7,11]. Gudjonsson's group found some psoriasis-specific DEGPs were enriched with IL-17A targets [9]. These studies have made the contributions to the development of the biological therapies for psoriasis. More studies with the multi-omics integration are needed for biomarker discoveries to achieve a new era of personalized medicine.

In this study, by integrating serum proteome and skin transcriptome, we observed that the peptidase inhibitor 3 (PI3) had the significant correlation between serum proteome and skin transcriptome. Previously, using multiple proteomics techniques with different cohorts of patients with psoriasis, we have shown that the serum protein levels of PI3 are significantly increased in patients with psoriasis, and the abundance of PI3 was positively correlated with the disease severity [12,13]. Some studies from other groups also showed that in psoriasis, the level of PI3 gene expression is increased in the lesions and PI3 protein levels are increased in serum [14–17]. However, none of these single-layer (only tissue-based or circulation-based) studies were able to connect the local skin and systemic circulation with PI3. Here we integrated different omics levels and used different independent cohorts to discover and validate biomarkers for psoriatic lesions. Our results indicate that the biomarkers of keratinization linked the skin with the circulation in psoriasis. And PI3 is associated with clinically relevant disease-outcome measures and relates to hyper-keratinization, the hall-mark feature of psoriasis immunopathology.

2. Materials and methods

2.1. Study design

This study was conducted at the University Medical Center Utrecht and performed in compliance with the Helsinki principles. Ethical approval was obtained from the institutional review board before the recruitment of participants. All participants signed written informed consent before participation. The cohort included psoriasis patients with a dermatologist-confirmed diagnosis of psoriasis, in whom concomitant psoriatic arthritis (PsA) was clinically excluded by a rheumatologist; patients with psoriasis and concomitant PsA (fulfilled classification of psoriatic arthritis criteria (CASPAR) [18]); patients with a clinical diagnosis of ankylosing spondylitis (AS) (fulfilled assessment of spondylo-arthritis international society classification criteria (ASAS) [19]) were included as a non-psoriatic, inflammatory disease reference group, none of which had a history of psoriasis. Sex- and age-matched healthy donors without any skin and rheumatic diseases were also recruited. The recruitment of participants was performed at the outpatient clinic of the Department of Rheumatology and Clinical Immunology.

In our previous studies [13,20], we found only slight differences between psoriasis and PsA at the serum protein and the skin transcriptome level. Here, we therefore combined samples of psoriasis and PsA patients in the psoriasis group.

We obtained and analyzed relevant data sets from public databases for validation and cell-type level profiling [9,12,21–23]. For the cell-type level analysis, we applied target gene expression profiling on the single-cell dataset from Haniffa's study [22] for skin tissue and from Haskamp's study [23] for peripheral blood mononuclear cells (PBMCs) (Supplementary table 1).

2.2. Evaluation of psoriasis severity at the site of biopsy

The PASI scoring method was performed to give a "local PSI" score for the site where biopsy of most-representative affected skin was performed (cumulative score of 0–12 based on the total sum: (0–4 redness) + (0–4 thickness) + (0–4 scaling)) [24].

2.3. RNA-seq analysis

Skin samples were derived from 4 mm punch biopsies, which were embedded in Tissue-Tek® and directly snap-frozen in liquid nitrogen, until further processing. After RNA isolation and library preparation, RNA sequencing was performed as previously published [20]. All samples passed the quality control. We stored our raw counts and metadata in the GEO database (GSE186063).

2.4. Serum proteomic analysis

Serum samples were collected, centrifuged at 1700 g for 10 min at 4 °C and stored directly at − 80 °C. As part of a larger overall study design, we performed proteomic analysis as previously published [13]. A total of 1012 proteins within 11 different Olink panels were detected in each sample. All data passed the Olink internal quality control. In our previous work, we worked on the landscape proteome profile of diseases and excluded two Pso patients due to their limit number of detected proteins [13]. However, in the current study, we focused on serum proteins that correlated with gene expression in tissue. Most of these proteins were detected in all samples. Therefore, we included all patients in the original cohort for this study.

2.5. Random forest (RF) and support vector machines (SVM) for feature selection

RF was used for feature selection preferentially because of its own interpretation of feature importance. Using the R package randomForest [25], classifiers were constructed for the clinical status of a sample for our proteome data: patient with psoriasis v.s. healthy individual; patient with psoriasis v.s. patient with AS; patient with psoriasis v.s. combination of healthy individual and patient with AS. The mean decrease accuracy and mean decrease in Gini impurity over all trees were estimated for the importance rank of the 47 serum proteins after 100 iterations.

To verify the performance of PI3, IL17C and their combination as classifiers for psoriasis, using the R package e1071 [26], we constructed SVM models for transcriptome data to classify the clinical status of a sample (psoriatic lesion, non-lesion (in our transcriptome data and two publicly available dataset: GSE67785 with 14 psoriatic lesions and 14 non-lesions, GSE83645 with 20 psoriatic lesions and 5 non-lesions), or AD skin (in a publicly available dataset GSE121212 with 28 psoriatic lesions and 27 AD lesion)). The recursive feature elimination (RFE) function was applied with the normalized expression of PI3 and, IL17C, both individually and in combination. Accuracy of SVM classification was calculated as the percentage of samples that were correctly classified. Repeated 6-fold cross-validation was performed using the caret R package to obtain the average classification accuracy [27]. The information of public datasets for validation was provided in supplementary table 1.

2.6. Single-cell transcriptome analysis

Single-cell data set was obtained from the ArrayExpress database (E-MTAB-8142) [22]. Data normalization, scaling, highly variable gene selection, principal component calculation and dimensionality reduction were all performed using scanpy (v1.8.2) [28]. Highly variable genes were detected with minimum cut-off values of 0.0125 and 0.5 for expression and dispersion, respectively. Batch correction (donor-to-donor variation) was adjusted using the bbknn package (v1.5.1) [29]. Cell-type annotation was based on gene expression profiles provided by the original author. All these analyses were performed in Python (v3.8.10) [30].

2.7. Immunohistochemistry

Sections cut to 4 µm with a LEICA RM2245 microtome (LEICA, Germany) were dried at 70 °C for 60 min and stained with anti-PI3 (Boster, mouse monoclonal, clone c7, diluted 1/300) on a Ventana BenchMark ULTRA immuno stainer (Ventana Medical Systems, Tucson, USA). The Ventana staining procedure included pretreatment with cell conditioner 1 (pH 8) for 24 min, followed by incubation with undiluted VE1 hybridoma supernatant at 37 °C for 32 min. Antibody incubation was followed by standard signal amplification including the Ventana amplifier kit, ultra-Wash, counterstaining with one drop of hematoxylin for 8 min and one drop of bluing reagent for 4 min. For chromogenic detection, OptiView DAB IHC Detection kit (Ventana Medical Systems) was used. Subsequently, slides were removed from the immunostainer, washed in water with a drop of dishwashing detergent, and mounted. Photomicrographs were taken with a NanoZoomer 2.0 HT (Hamamatsu, Japan).

2.8. Statistical analysis

For clinical characteristics, the chi-square test was applied for non-continuous variables, and analysis of variance (ANOVA) for continuous variables. For differential expression analysis of the transcriptome data, a likelihood ratio test (LRT) was applied for multivariable comparisons and DESeq2 (version 1.32.0) for pair-wise comparisons [31]. For differential abundance analysis of the proteome data, LRT was applied with limma (version 3.50.0) [32]. All correlations were based on Spearman's rank correlation coefficients. P values < 0.05 were considered significant. Adjusted *P* values were corrected using the Benjamini-Hochberg (BH) method [33]. All statistical analyses were performed using R (version 4.0.3) (http://cran.r-project.org/).

3. Results

3.1. Patient cohorts

A cohort of 20 patients with psoriasis, 20 patients with PsA, 19 patients with AS and 20 healthy donors was included in this prospective observational study (N = 79). All these groups were matched for age and sex. C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR), two biomarkers commonly used to detect inflammation, were not significantly different between the patient groups. The clinical characteristics of the participants are shown in Table 1. For proteomic analysis, serum samples were available from all donors. For transcriptome analysis, lesion and non-lesion were obtained from 12 patients with psoriasis and 15 patients with PsA. Healthy skin biopsies were obtained from 12 patients with AS.

3.2. Gene expression level of PI3 in skin positively correlated with its corresponding circulating protein

Previously, we performed differential expression analysis of skin transcriptome and serum proteome data separately [13,20]. To explore the systemic aberrations caused by psoriasis, in this study we integrated the serum proteome and skin transcriptome data to study the correlation between RNA expression and the corresponding protein levels. A total of 866 gene-protein pairs were available for the analysis. 57 out of these 866 gene-protein pairs correlated between the two layers (serum protein and gene expression level of lesional skin) (Fig. 1. A). However, after the adjustment for multiple comparison tests, only PI3 showed the significant correlation, with the highest coefficient (r = 0.67; P = 0.000056, FDR = 0.049) (Fig. 1. B).

3.3. PI3 positively correlated with disease severity

We then investigated the association between PI3 and clinical disease severity as measured by PASI and local PSI (the severity of the lesion from which the biopsy was taken). We found that both the gene and protein expression levels of PI3 were significantly positively correlated with PASI and local PSI (PI3 gene with PASI: r = 0.45, P = 0.015, FDR = 0.015; with local PSI: r = 0.62, P = 0.00043, FDR =

Table 1
Clinical characteristics of the participants.

	Psoriasis (n = 20)	PsA (n = 20)	AS (n = 19)	HC (n = 20)	*P* value
Sex					
female	8 (40.0%)	7 (35.0%)	5 (26.3%)	7 (35.0%)	0.841
male	12 (60.0%)	13 (65.0%)	14 (73.7%)	13 (65.0%)	
Age (years)	38.4 (15.5)	41.9 (9.11)	40.5 (12.3)	43.6 (12.7)	0.520
BMI (kg/m^2)	29.2 (7.44)	27.7 (4.54)	24.2 (3.41)	-	0.0420*
PASI	2.80 (5.30)	3.00 (3.70)	-	-	0.516
Pso duration (years)	12.4 (12.7)	20.0 (20.2)		-	0.537
PsA duration (years)	-	0.629 (7.55)		-	
AS duration (years)	-	-	5.58 (10.9)	-	
CRP (mg/L)	2.75 (4.10)	2.80 (1.90)	3.15 (5.98)	-	0.667
ESR (mm/hour)	5.50 (6.25)	5.00 (10.5)	5.00(10)	-	0.870
DMARD history					
Yes	3 (15.0%)	6 (30.0%)	2 (10.5%)	-	0.259
No	17 (85.0%)	14 (70.0%)	17 (89.5%)	-	
UVB history					
Yes	10 (50.0%)	11 (55.0%)	-	-	0.752
No	10 (50.0%)	9 (45.0%)	-	-	

Mean (standard deviation) are presented for normally distributed continuous values (age and BMI). Median (interquartile range) are presented for non-normally distributed continuous values (PASI, durations, CRP and ESR). Frequencies (proportion) are presented for categorical values. DMARD or UVB history: usage in past 3 months.
* Significant at *P* value < 0.05.

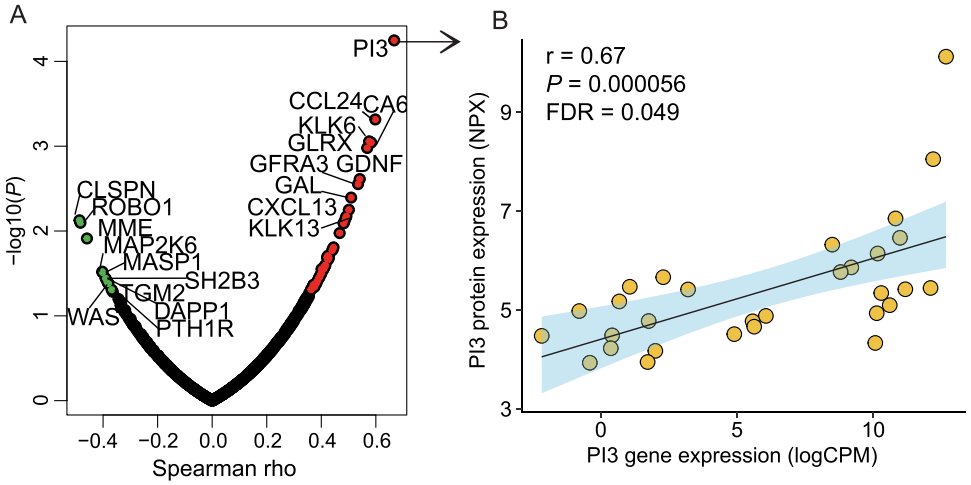

Fig. 1. Gene-protein correlation profiles. A. Gene-protein correlations in psoriasis, PsA and AS. The red dots are for positive correlations between gene expression and corresponding protein abundance, with *P* value smaller than 0.05. The green dots are for significant negative correlations between gene expression and corresponding protein abundance, with *P* value smaller than 0.05. The correlations with top 10 coefficient (positive or negative) were labeled with names. B. Gene-protein correlation of PI3.

0.00087. PI3 protein with PASI: $r = 0.72$, $P = 0.00030$, FDR = 0.00087; with local PSI: $r = 0.64$, $P = 0.0020$, FDR = 0.0026) (Fig. 2).

3.4. PI3 is specifically expressed in skin lesions and serum of patients with psoriasis

To evaluate the potential of PI3 as circulating cell-free biomarkers in psoriasis, we used the other 46 proteins which correlated with their genes with *P* value smaller than 0.05 but FDR greater than 0.05 as competitors, and applied random forest algorithm to rank the feature importance of these 47 proteins. We observed that PI3 achieved greatest mean decrease accuracy and mean decrease gini in classifying psoriasis versus AS or non-psoriatic condition (combination of AS and healthy control) (Fig. 3. A, Fig. S1). When classifying psoriasis versus healthy control, the rank of PI3 was behind the ranks of ITGB6 and GAL. We checked the expression of ITGB6 and GAL. When comparing with the healthy control, both of them were decreased in psoriasis, while PI3 was increased (Fig. S2).

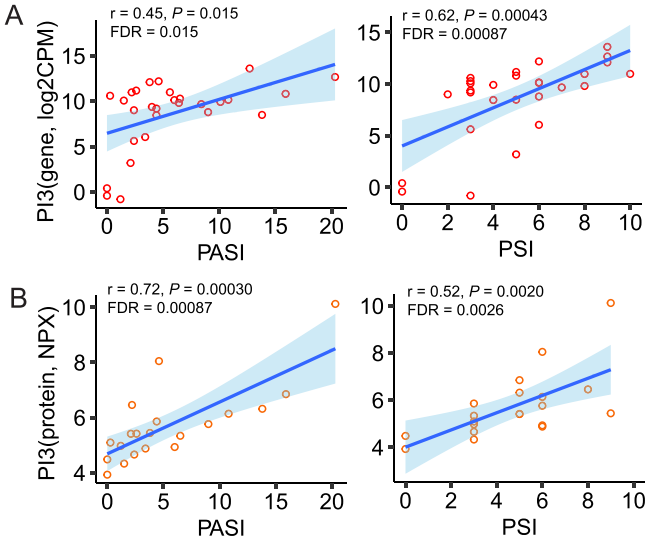

Fig. 2. The correlation between the expression of PI3 and disease severity in psoriasis. A Correlation between gene expression and disease severity PASI (left) or PSI (right) in psoriasis. B Correlation between protein abundance and disease severity PASI (left) or PSI (right) in psoriasis. Two patients were considered to be in remission when the biosamples were token.

To investigate the value of PI3 in gene expression level, we then constructed SVM with the expression of PI3, IL17C and their combination to classify the clinical status of a sample with RNA-seq datasets. We observed that PI3 achieved greater accuracy in classifying psoriasis versus healthy than IL17C (and even than their combination). This finding was validated in other three independent cohorts (Fig. 3. B). Furthermore, the PI3 classifier performed well in distinguishing patients with psoriasis from patients with AS based on serum proteomic data. For the discrimination between lesions of psoriasis and lesions of AD (based on GSE121212), the PI3 classifier also reached greater accuracy than IL17C classifier and PI3-IL17C classifier.

3.5. PI3 is specifically expressed by keratinocytes in psoriatic lesions

To better understand the role of PI3 in the disease pathogenesis at the site of lesions, and especially which cell types secreted PI3, we studied PI3 in two publicly available single-cell sequencing datasets: one for skin tissue (E-MTAB-8142, 3 lesion v.s. 3 non-lesion) [22], the other for PBMCs (GSE182244, 3 patients vs 3 healty donor) [23].

We found that PI3 was highly expressed in lesional skin samples taken from psoriasis patients, lowly expressed in lesional skin samples from atopic dermatitis (AD) patients, and rarely expressed in healthy skin (Fig. 4. A, B). Notably, PI3 was selectively expressed by the three subsets of keratinocytes in psoriatic lesions, while undifferentiated keratinocytes had the highest expression level of PI3 (Fig. 4. C). Using an independent cohort (GSE182244), in which single cell sequencing was performed by isolating PBMCs from patients with psoriasis and healthy controls, we found that PI3 was not expressed in any of the cell subsets from PBMCs. This suggests that the aberrations observed in the level of PI3 in serum of psoriasis patients are potentially due to the skin disease. These findings suggest that PI3 detectable in serum could be used as a biomarker of psoriasis immunopathogenesis, specifically reflecting local hyperkeratinization.

We then applied immunohistochemical staining to visualize the expression of PI3 of protein level in skin tissue section from a patient with psoriasis (Fig. 5. A). We found a positive expression of PI3 in the epidermis of lesion from patient with severe psoriasis (PASI = 10.8, PSI = 6) (Fig. 5. B). A zoom of the area framed in red on epidermis mainly gave a strong positive expression of PI3 in the cytoplasm of keratinocytes in the stratum spinosum (Fig. 5. C). The expression of

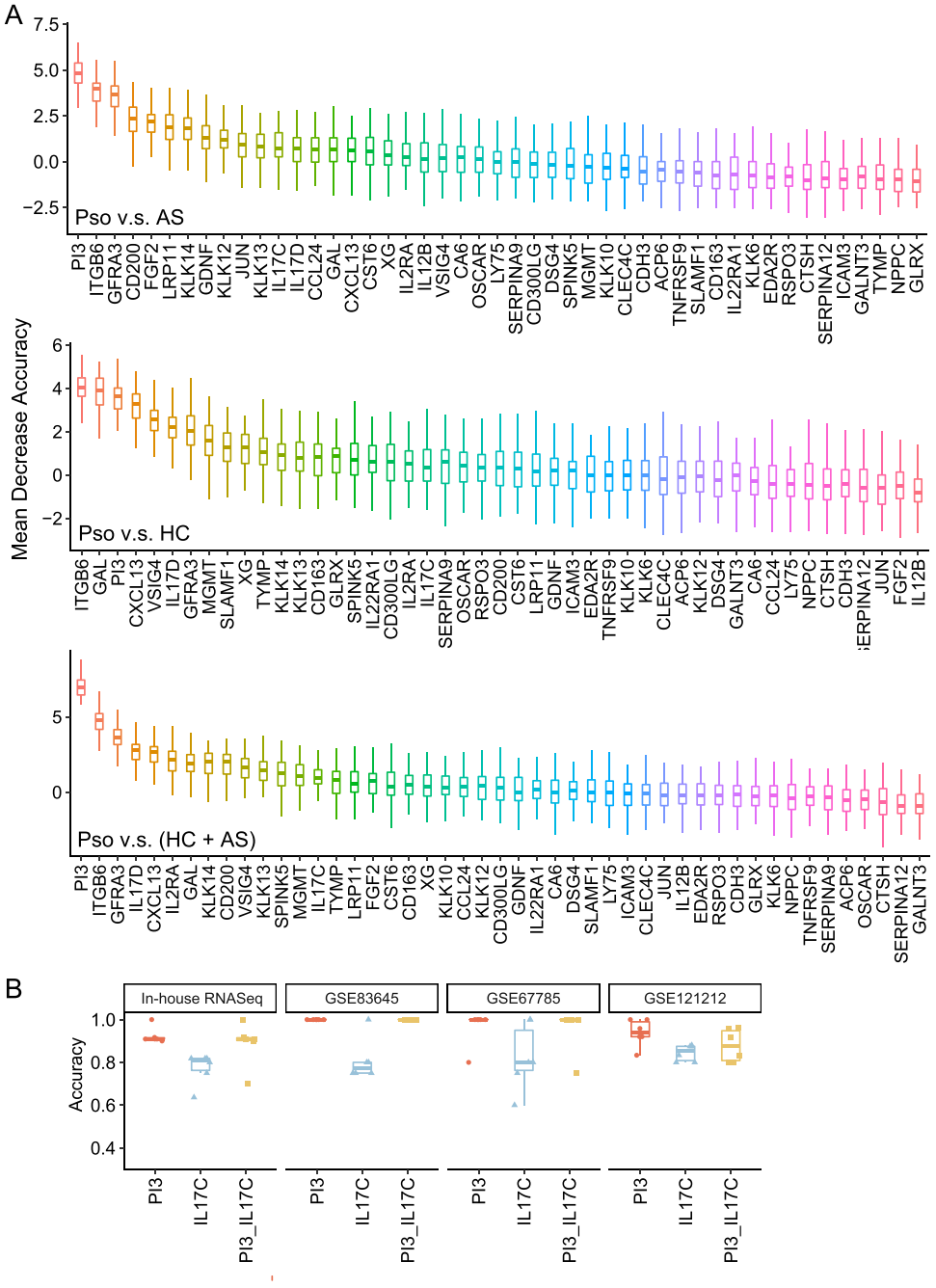

Fig. 3. RF and SVM classification of psoriatic and non-psoriatic conditions. A. The feature importance of RF classifiers with individual proteins for psoriatic, AS, healthy control (HC) and non-psoriatic (AS and HC combined) samples psoriatic and non-psoriatic samples in our serum Olink data. B. The performance of SVM classifiers for psoriatic and non-psoriatic samples, with PI3, IL17C and their combination.

PI3 gradually weakens toward from the center of the lesion (left) to the boundary of the lesion (right).

4. Discussion

To date, no single laboratory test exists that accurately measures the severity in psoriasis, although numerous biomarkers have been proposed [34,35]. By integrating multi-omics approaches, we aimed to identify the most promising biomarker(s) in serum that reflect both clinical disease severity and local immunological aberrances of the psoriatic lesions. We identified the increased PI3 transcripts in the skin correlated strongly with increased PI3 protein levels in the serum within the same cohort. This correlation implied the potential of PI3 as a circulating cell-free biomarker in psoriasis. We also found that PI3 was associated with local and global severity in psoriasis, both at the gene and at the protein level.

PI3 is a neutrophil and elastase-specific inhibitor that can prevent elastase-mediated tissue proteolysis. It is also an antimicrobial peptide. The inhibitory function against neutrophil-derived serine proteinases makes PI3 a vital part in the pathophysiology of psoriasis. It has been shown that serum PI3 levels correlated with PASI scores in our previous studies [12,13]. Our current study tends to focus on the expression level of PI3 in psoriatic skin tissue and its impact on serum PI3 levels, rather than the serum PI3 levels simply. Therefore, we believe that our study provides a novel perspective on the role of PI3 in psoriasis and expands the current knowledge in this field. To confirm the specific expression of PI3 in psoriasis, we included not only healthy individuals, but also people with the skin

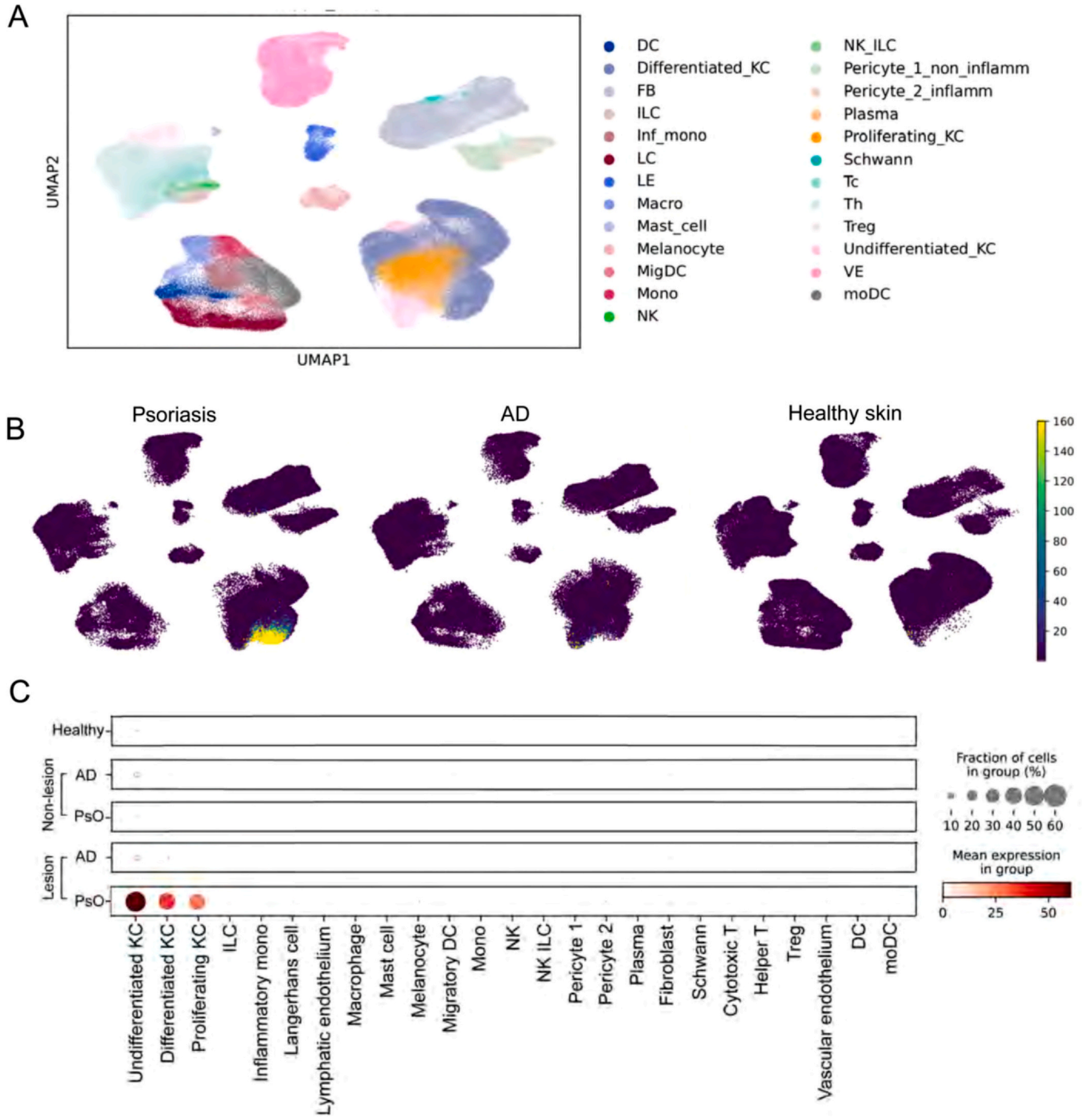

Fig. 4. Gene expression profiling of PI3 at single-cell level. A. UMAP for the cell type annotation of skin single-cell transcriptome data. B. Expression of PI3 in different cohorts. C. Gene expression of PI3 in different cell-types across different conditions. KC: keratinocyte, FB: fibroblast, VE: vascular endothelium, LE: lymphatic endothelium, Tc: cytotoxic T cell, Th: T helper cell, Mac: macrophage, Inf.: inflammatory, LC: Langerhans cell, Mig.: migratory, MoDC: monocyte derived dendritic cell.

disease AD or the rheumatic disease AS in the control group. By constructing machine learning classifiers, we found that the PI3 was the best predictor for psoriasis among all classifiers. This finding is similar to Krueger's finding that based on protein PI3 levels in serum with lipocalin 2 (LCN2) one can differentiate psoriasis from hidradenitis suppurativa [11]. In psoriatic lesions, PI3 was shown to hinder the communication between elastin peptide and its receptors on neutrophils and thereby restrains neutrophil chemotaxis and inflammatory processes in the tissue [36]. One possible explanation for these seemingly contradictory findings is that it is a defensive activity to counteract the excessive neutrophil elastase activity and inflammation in psoriatic skin. However, this may not be sufficient or effective enough to prevent or resolve the disease. Although PI3 has antimicrobial effects, it is also involved in promoting inflammation. In our previous study, we integrated skin transcriptome and microbiome data and found that PI3 was involved in a core network of psoriasis [20]. This network is related to both inflammation and hyper-keratinization in psoriatic skin. We suspect that the increase of PI3 in psoriatic skin is due to the defensin-like antimicrobial activity of keratinocytes, which is induced by microbial imbalances in psoriatic skin. So, our hypothetical conclusion for PI3 in psoriasis is that, PI3 is produced in excess, and this may lead to

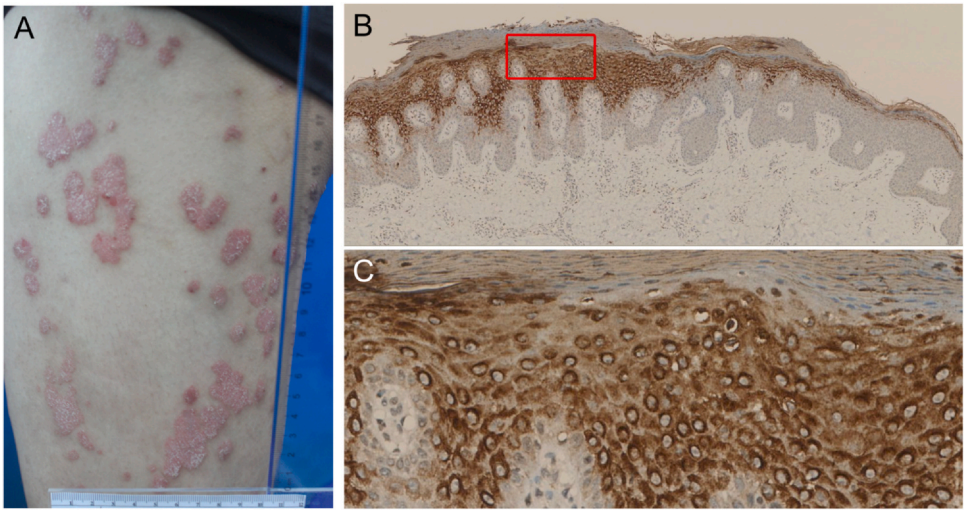

Fig. 5. Histo-immune expression of PI3 in the skin from patients with psoriasis. A Photo of psoriatic lesion in left leg that underwent a biopsy. B Expression of PI3 in the skin from a patient with severe psoriasis (PASI = 10.8, PSI = 6, magnification: 20 fold). C Positive expression of PI3 in the cytosol of keratinocytes in stratum spinosum of skin from a patient with severe psoriasis (Zoom corresponding to the red rectangle in Fig. 5A, magnification: 400 fold).

a feedback loop that perpetuates the cycle of inflammation and skin cell proliferation seen in the disease.

Importantly, by in-situ staining with skin from patient with severe psoriasis, we confirmed the expression specificity of PI3 in the cytoplasm of keratinocytes in the stratum spinosum. This finding supports the potential of PI3 as a biomarker for the abnormal keratinocyte proliferation. Abnormal keratinocyte proliferation is the main pathophysiological characteristic of psoriasis. This evaluation of PI3 can be translated to clinical applications, such as diagnosis, recurrence, and therapy of psoriasis. Skin biopsy testing is currently the gold-standard assessment for hyper-keratinization in psoriatic lesions, but is invasive, expensive, and limited to local lesion measurement. Evaluating hyper-keratinization based on blood biochemical measures could be less invasive, cheaper, and more systemic. With single-cell analysis, we demonstrated that the expression of PI3 was keratinocyte-specific, suggesting the secretion of PI3 from psoriatic epidermis to the skin capillaries, and ultimately in circulation. It can be used to monitor disease progression and to guide appropriate treatment before symptoms in skin appear.

4.1. Limitations

A limitation of our study is that the biomarker discovery design does not permit causal inference. Also, in the proteomic study, we started with a total of 1012 protein candidates, which do not cover all potential biomarker proteins of interest.

5. Conclusion

In conclusion, based on parallel analysis of multi-omics data and public data sets at protein and transcript levels, we have identified PI3 as a potential biomarker for disease severity in psoriasis, which can be detected both in the skin and in the circulation.

Ethical approval

Ethical approval (MvdL/nb/15/041945) was obtained from the institutional review board before the recruitment of participants. All participants signed written informed consent before participation.

Fundings

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CRediT authorship contribution statement

Jingwen Deng: Conceptualization, Methodology, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. **Emmerik Leijten:** Conceptualization, Methodology, Formal analysis, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing. **Yongzhan Zhu:** Data curation, Formal analysis, Writing – review & editing. **Michel Olde Nordkamp:** Resources, Writing – review & editing. **Shuyan Ye:** Resources, Writing – review & editing. **Juliëtte Pouw:** Resources, Writing – review & editing. **Weiyang Tao:** Data curation, Writing – review & editing. **Deepak Balak:** Resources, Writing – review & editing. **Guangjuan Zheng:** Resources, Writing – review & editing. Timothy Radstake Funding acquisition, Supervision, Writing – review & editing. **Ling Han:** Resources, Writing – review & editing. **José A.M. Borghans:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Chuanjian Lu:** Methodology, Supervision, Resources, Writing – review & editing. **Aridaman Pandit:** Conceptualization, Funding acquisition, Project administration, Supervision, Resources, Writing – review & editing.

Data Availability

The skin transcriptome data used in the analysis is available in GEO database (GSE186063).

Declaration of Competing Interest

TR, AP and WT is currently an employee of AbbVie, with no conflicts of interest regarding the work of this manuscript. The other authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdermsci.2023.07.005.

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