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Serum Proteomic Profiling Uncovers Dysregulated Keratinisation and Immune-Related Pathways in Hidradenitis Suppurativa

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ABSTRACT

Hidradenitis suppurativa (HS) is an autoinflammatory keratinisation disease affecting the pilosebaceous unit and hallmarked by a complex and multifactorial pathogenesis. Although genomic and transcriptomic investigations have substantially advanced our understanding of key mechanisms underlying HS pathogenesis, proteomic studies remain limited, despite the significant potential of serum proteomics to identify molecular signatures reflecting both cutaneous and systemic inflammatory activity. This exploratory study presents a serum proteomic analysis of patients with moderate-to-severe HS, identifying 306 differentially abundant proteins out of 3153 profiled (FDR $q < 0.10$). Sensitivity analysis at $q < 0.05$ (194 proteins) confirmed a robust inflammatory signature, while the FDR $q < 0.10$ threshold was necessary to preserve markers of epidermal homeostasis, which are inherently diluted in systemic circulation. Enrichment analyses revealed dysregulated pathways related to keratinisation, epidermal differentiation and extracellular matrix (ECM) remodelling, indicating impaired skin barrier function. Concurrent higher abundance of immune-related pathways, including defence response to bacterium, complement activation and neutrophil degranulation, suggest systemic inflammation potentially linked to microbial dysbiosis. These findings suggest the dual role of epithelial dysfunction and autoinflammation in HS pathogenesis. Integration of proteomic data with genomic and transcriptomic findings underscores the value of multi-omics approaches in guiding targeted therapeutic development.

1 | Background

Hidradenitis suppurativa (HS) is a chronic, auto-inflammatory skin disorder of the terminal hair follicle unit, affecting body areas such as axillary, inguinal, genital or inframammary regions. HS affects both adults and, notably, younger populations, considering that almost half of patients note their first symptoms in childhood, and paediatric patients account for nearly one-third of all cases [1]. HS pathogenesis is driven by the interplay of genetic, immunological, environmental and

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microbial factors that lead to hair follicle plugging and cyst formation, but our understanding of how these factors shape disease pathogenesis is still limited [2, 3]. Repeated chronic inflammation in patients promotes disease progression to a severe stage, which is associated with interconnected epithelialised tunnel formation, extensive scarring and numerous immune cells and inflammatory mediators that contribute to tissue destruction [3]. Insights into the genetic predisposition of HS primarily came from familial cases, revealing mutations in γ-secretase genes that lead to follicular occlusion, disturbed keratinisation and upregulated autoinflammation. Also, sporadic forms of HS have a genetic background that contributes to its susceptibility, thus supporting a multifactorial aetiology [4–6].

More recent evidence suggests the emergence of a complex inflammatory polygenic architecture involving multiple genetic variants linked to epidermal differentiation, extracellular matrix (ECM) organisation and immune response [7, 8]. Transcriptome analyses also suggest that upregulated inflammation, epidermal barrier dysfunction and dysregulated metabolism signalling pathways are major contributors to disease pathogenesis [9, 10]. While genetics and transcriptomics are contributing to elucidating several crucial patho-mechanisms, proteomic studies remain scarce, even though serum proteomics hold great potential to capture systemic molecular signatures reflecting both cutaneous biology and systemic inflammation.

2 | Questions Addressed

- Given a still limited application of proteomics in HS, can serum proteomic profiling identify novel, quantifiable systemic molecular signatures that reliably reflect the cutaneous pathology and overall inflammatory burden of the disease?
- Which specific biological pathways are significantly dysregulated in the HS serum proteome?
- Can serum proteomic profiling in moderate-to-severe HS patients identify a distinct systemic molecular signature that differentiates them from healthy controls and reflects the combined cutaneous and systemic aspects of the disease?

3 | Experimental Design

To investigate systemic alterations, we conducted proteomic profiling in a well-characterised cohort of moderate-to-severe HS patients.

Twelve patients with moderate-to-severe HS, without comorbidities, were enrolled at the Dermatology Unit of Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan. Patients were categorised according to Hurley staging [11] and the International Hidradenitis Suppurativa Severity Score System (IHS4) [12] to assess disease severity and clinical heterogeneity. Patient clinical characteristics, including BMI, smoking status, concomitant comorbidities, age at HS onset and diagnosis, Hurley stage, IHS4 score and current topical and systemic therapies, are reported in Table 1.

Following the clinical examination, peripheral blood sampling was performed. Eleven healthy controls (HCs), matched by ethnicity, gender and age, were also enrolled.

Serum was processed from blood collected in anticoagulant-free tubes and stored at −80°C. Following the depletion of high-abundance proteins using ProteoMiner TM columns, 20 μg of proteins were digested using the EasyPep TM MS Sample Prep Kit.

ProteoMiner-based depletion efficiency was evaluated by SDS-PAGE (gel 4%–10%) analysis of crude and depleted serum samples. The gel was transferred to a fixing solution containing (40% ethanol and 10% acetic acid) and stained with SYPRO Ruby for 12 h. The gel was then rinsed in a solution of 10% ethanol and 7% acetic acid. Finally, the gel was scanned using a Bio-Rad Pharos scanner. Peptide separation was performed using an EASY-nLC system coupled to an Orbitrap Fusion Lumos mass spectrometer (Thermo Fisher Scientific). Peptides were separated on an EASY-Spray HPLC column (75 cm length × 75 μm i.d., C18, 2 μm particles, 100 Å pores) at a flow rate of 300 nL/min. The mobile phases consisted of solvent A (0.1% FA in water) and solvent B (0.1% FA in ACN). The LC gradient was a linear increase from 1% to 45% B over 150 min, followed by a wash at 99% B for 24.4 min.

Data were acquired in positive ion mode (range 400–1000 m/z) using 50 variable isolation windows (average width ~ 12 m/z). The total cycle time was 3 s. Full MS scans and MS/MS scans were acquired at resolutions of 60 000 and 30 000 (at m/z 200), respectively. Higher-energy collisional dissociation (HCD) was employed with a normalised collision energy (NCE) of 30, and the m/z range was set to 375–1500 m/z. Finally, data independent acquisition (DIA) was processed with Spectronaut 19 (directDIA, FDR < 1%, ≥ 1 unique peptide).

PCA was performed using the prcomp function in R. To ensure that high-abundance proteins did not disproportionately influence the components, the data were centred and scaled prior to the PCA.

Hierarchical clustering was performed on log2-transformed and *Z*-score scaled protein intensities. Dissimilarity between proteins and samples was calculated using Euclidean distance, and clusters were generated using the complete linkage method via the heatmap R package.

Differential abundance was assessed using the Mann–Whitney *U*-test for all pairwise comparisons between HS patients and healthy controls, and *p*-values were adjusted for multiple testing using the Benjamini-Hochberg procedure (FDR). An adjusted $q < 0.05$ and fold change > 1.5 or < 0.667 were used to define differentially abundant proteins (DAPs). To ensure a comprehensive overview of the biological pathways involved in Hidradenitis Suppurativa, functional enrichment analysis was performed on an expanded set of candidate proteins exhibiting an adjusted q value < 0.10. This secondary threshold was adopted to minimise the loss of biologically relevant proteins that may not reach strict FDR-adjusted significance due to the modest sample size, while still maintaining an exploratory threshold standard in discovery proteomics. Protein functional annotation was carried out using Reactome and g:Profiler. g:Profiler automatically applies the

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TABLE 1 | Clinical characteristics of HS patients enrolled in the study.

Patient ID/Sex	BMI	Smoking	Concomitant comorbidities	Age at HS onset	Age at HS diagnosis	Clinical phenotype[a]	Hurley stage at the time to enrolment	IHS4 at the time to enrolment	Main topic and systemic therapies at the time to enrollment	Time (days/weeks) of wash-out prior to enrolment
001/F v	23.88	+	None	22	23	Regular	II	6	Topical clarithromycin and lymecycline	4 weeks
002/F	23.44	−	None	14	14	Regular	III	9	Topical clarithromycin; topical and systemic clindamycin	4 weeks
003/M	23.55	+	None	17	18	Regular	III	8	Azithromycin	4 weeks
004/M	22.79	+	None	38	38	Regular	II	5	Topical and systemic clindamycin	6 weeks
005/M	28.29	+	None	15	18	Regular	III	10	Doxycycline, fusidic acid + betamethasone	10 weeks
006/M	23.53	+	None	30	34	Regular	III	12	Anti-IL-17 inhibitor (secukinumab)	12 weeks
007/M	23.12	+	None	25	30	Regular	II	16	Anti-TNF (adalimumab)	12 weeks
008/F	28.21	+	None	13	23	Regular	III	12	Anti-TNF (adalimumab)	12 weeks
009/F	22.31	+	None	43	45	Regular	III	16	Anti-TNF (adalimumab)	12 weeks
010/F	22.45	+	None	29	31	Regular	III	19	—	—
011/F	27.40	+	None	19	22	Regular	III	16	—	—
012/M	22.76	+	None	36	36	Regular	III	12	Anti-IL-17 inhibitor (secukinumab)	12 weeks

Abbreviations: BMI, body mass index; HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; IL, interleukin; TNF, tumour necrosis factor.
[a]According to van der Zee classification.

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Benjamini-Hochberg to control the FDR across GO Biological Process (BP), Cellular Component (CC) and Molecular Function (MF) categories. Similarly, the Reactome platform utilises the Benjamini-Hochberg (BH) procedure by default. Visualisations (bubble plots and bar charts) were generated using SRplot (bioinformatics.com.cn). All the analyses were performed within RStudio.

To validate the proteomic findings, orthogonal validation was performed via Western Blot (WB) analysis on two representative differentially abundant proteins (DAPs) (Lactoferrin, LTF and Aldolase B, ALDOB). Protein samples were separated on Bio-Rad gradient gels (4%–10%). The proteins were then transferred on nitrocellulose membranes employing the TransBlot Turbo Transfer System (Bio-Rad). Membranes were incubated with Primary antibodies against LTF (PA5-95513, Invitrogen) and ALDOB (HPA002198, Sigma) and then with HRP-conjugated secondary antibodies. ClarityTM substrate (Bio-Rad) was used and chemiluminescent detection was acquired with the ChemiDoc imaging System (Bio-Rad). Membranes were stained with Ponceau S solution to evaluate total protein loading. Densitometric analysis of the bands was performed using ImageJ.

4 | Result

ProteoMiner-based depletion efficiency was evaluated by SDS-PAGE analysis of crude and depleted serum samples (Figure 1). The depleted samples showed a reduced abundance of high-abundance proteins and enhanced enrichment of lower-abundance proteins.

We profiled 3153 proteins from HS patients and age-matched HCs. Principal Component Analysis (PCA) was performed to evaluate the overall structure of the proteomic data. Visual inspection of the first two principal components, which accounted for approximately 50% of the total variance, revealed no significant outliers within the cohort (Figure 2a); the PCA scores plot demonstrated a clear separation with no overlap between HS patients and HCs along the primary axis of variation (PC1) (Figure 2b). This segregation underscores a distinct and robust proteomic signature intrinsically associated with the disease state.

Overall, we identified a total of 306 Differentially Abundant Proteins (DAPs), with 171 highly abundant and 135 less abundant proteins, as represented in the heat map (Figure 2c,d and Table S1).

A sensitivity analysis performed at a more restrictive threshold (FDR $q < 0.05$; Table S2) identified 194 proteins. While the inflammatory component of the signature remains stable at this level, the markers associated with epidermal homeostasis were found to be more sensitive to thresholding, supporting the use of an exploratory FDR $q < 0.10$ cutoff to preserve the biological connectivity of the epithelial-immune axis.

Gene Ontology (GO) terms were analysed across its three distinct ontologies: Molecular Function (MF), Biological Process (BP) and Cellular Component (CC) (Figure 3a). In the MF category, differentially abundant proteins in HS patients' group were significantly enriched for structural constituents of skin epidermis (GO:0030280), thus indicating an enhanced epidermal turnover. BP analysis further supported disruption of epidermal barrier

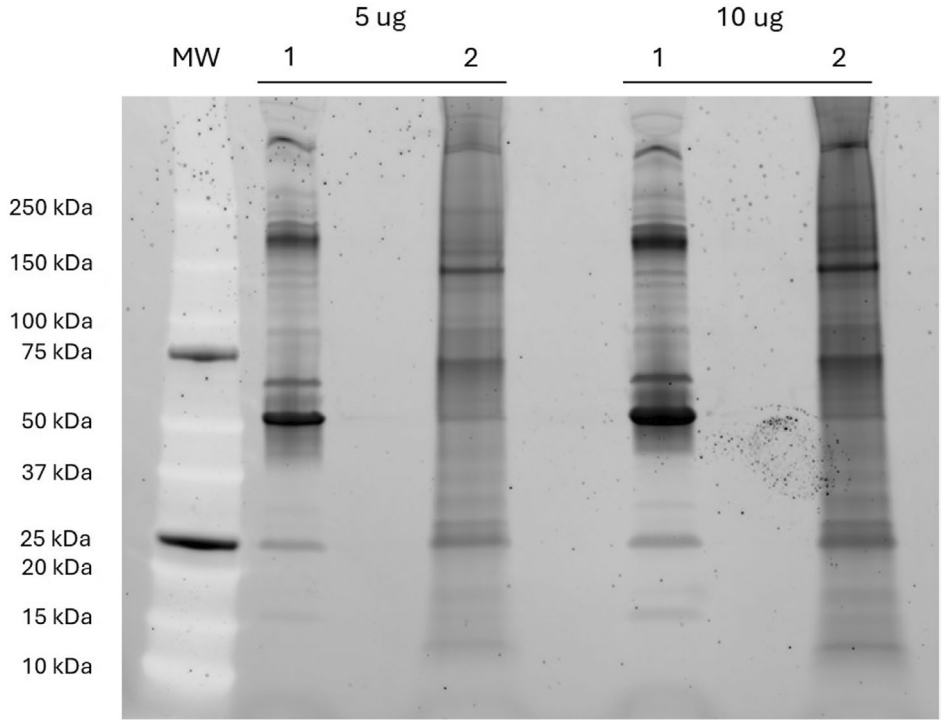


FIGURE 1 | ProteoMiner-based depletion efficiency. SDS-PAGE analysis of crude (lane 1) and ProteoMiner-depleted (lane 2) serum samples loaded at 5 and 10 μg. A strong reduction of high-abundance proteins, including serum albumin (~66 kDa), is observed in depleted samples, with enhanced detection of lower-abundance proteins.

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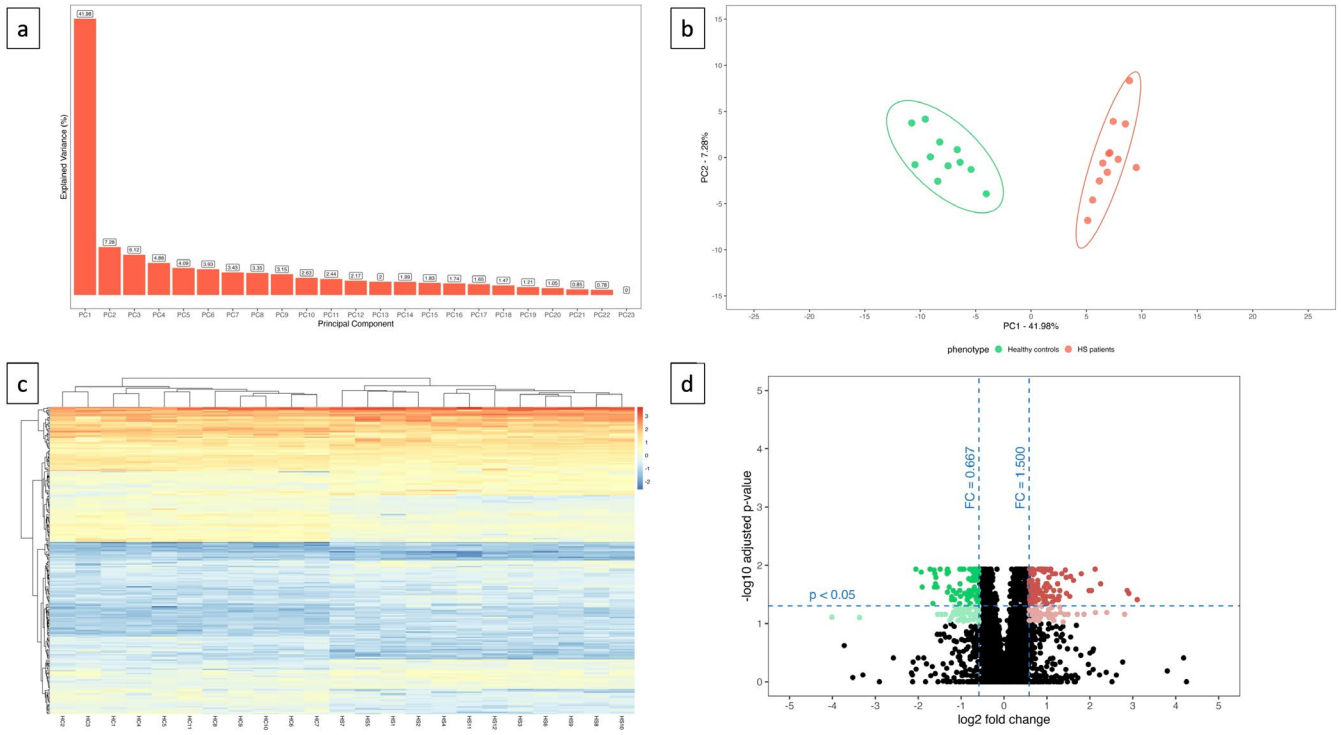


FIGURE 2 | Principal component analysis (PCA) plot of samples and heat map of the differentially abundant proteins (DAPs) in HS patients and age-matched healthy controls (HCs). (a) The scree plot illustrates the proportion of total variance captured by each principal component in descending order, highlighting the relative contribution of each dimension derived from the PCA. (b) Principal Component Analysis (PCA) biplot of DAPs of the two first principal components of the dataset. The first and second components explain 41.98% and 7.28% of the variation, respectively. Distinct colours correspond HS patients (red) and healthy controls (green) and a 95% Confidence Interval ellipse around the clusters (c) Heat map of DAPs with hierarchical clustering of samples and proteins. Colour intensity represents standardised protein abundance (red = higher expression; blue = lower expression), with hierarchical clustering applied to both rows and columns. (d) Volcano plot of the discovery proteins. Darker red and green colours correspond to differentially abundant proteins between hidradenitis suppurativa patients and clinically healthy controls at a significance level of $q < 0.05$ (FDR adjusted q value) and fold change > 1.50 or < 0.667. Meanwhile, the lighter green/red coloured points correspond to proteins with the same fold change threshold but at a significance level (FDR adjusted q value) < 0.10.

homeostasis and keratinisation, with significant enrichment of intermediate filament organisation (GO:0045109), keratinisation (GO:0031424), skin and epithelial development (GO:0043588; GO:0008544) and keratinocyte, epithelial and epidermal cell differentiation (GO:0030216; GO:0030855; GO:0009913). These findings are consistent with previous reports implicating early keratinisation abnormalities in HS pathogenesis [13, 14].

Immune-related pathways were also prominently represented. Enrichment of defence response (GO:0006952), defence response to other organism (GO:0098542) and defence response to bacterium (GO:0042742) supports the concept of sustained innate immune activation and microbial dysbiosis in HS15. Altered cutaneous microbiome composition and heightened immune reactivity are increasingly recognised as contributors to perifollicular inflammation in HS [15]. In line with this, our previous genetic analysis of an HS family identified a convergent role for antimicrobial defence pathways and dermcidin (DCD) in both HS etiopathogenesis and maintenance of microbiome equilibrium [16].

Within the CC ontology, enrichment of extracellular matrix (GO:0031012), collagen-containing ECM (GO:0062023), keratin filament (GO:0045095) and cornified envelope (GO:0001533) pointed to active tissue remodelling and differentiation. Experimental HS skin models have demonstrated that matrix metalloproteinase (MMP)-mediated ECM alteration may amplify inflammation through the release of bioactive fragments, ultimately contributing to fibrosis and hypertrophic scarring in chronic disease stages [17, 18]. Reactome pathway analysis (Figure 3b) corroborated these findings, identifying significant enrichment in keratinisation (R-HSA-6805567), cornified envelope formation (R-HSA-6809371), keratinocyte differentiation in interfollicular epidermis (R-HSA-9725554), as well as complement activation (R-HSA-166663; R-HSA-166658) and neutrophil degranulation (R-HSA-6798695). Collectively, these data reinforce the view of HS as an autoinflammatory keratinisation disorder characterised by impaired barrier homeostasis [19, 20], dysregulated complement activation and neutrophil transendothelial migration [21], and active participation of keratinocytes as amplifiers of inflammatory signalling [22].

From a translational perspective, the integrated proteomic signature delineates biologically coherent candidate actionable axes than a single definitive therapeutic target. First, a robust complement/neutrophil-driven inflammatory axis is supported by the enrichment of complement cascade and neutrophil degranulation pathways, and further validated by the significant increase in LTF abundance. This reinforces the hypothesis that pharmacologic modulation of complement activation or

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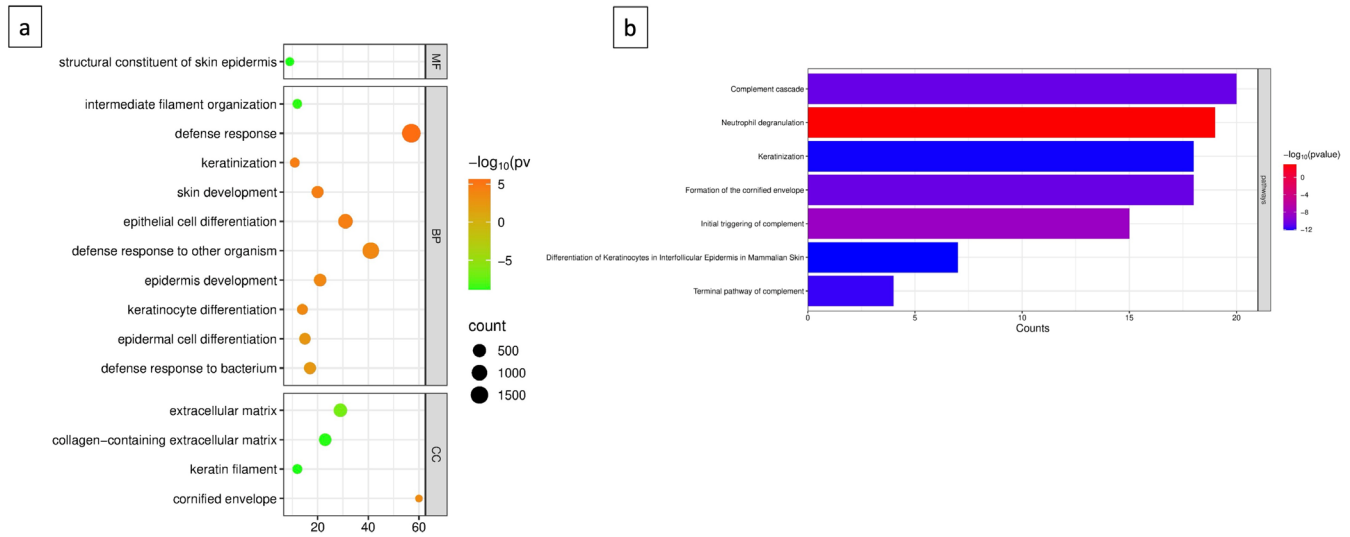


FIGURE 3 | Gene Ontology (GO) and Reactome enrichment analyses of DAPs. (a) GO functional annotation histogram of the DAPs. Analyses were performed using the expanded discovery set of 306 proteins as input against a background set consisting of all proteins identified and quantified in the MS experiment. The GO annotations are classified in three different basic categories including cellular component (CC), biological processes (BP) and molecular function (MF). Dot size represents the number of proteins (count), and colour intensity reflects statistical significance after Benjamini-Hochberg (BH) correction (adjusted q-value < 0.05). (b) The Reactome pathway enrichment analysis of DAPs. Bar colour indicates the adjusted q-value < 0.05 (BH procedure); the x-axis shows the number of proteins associated with each pathway.

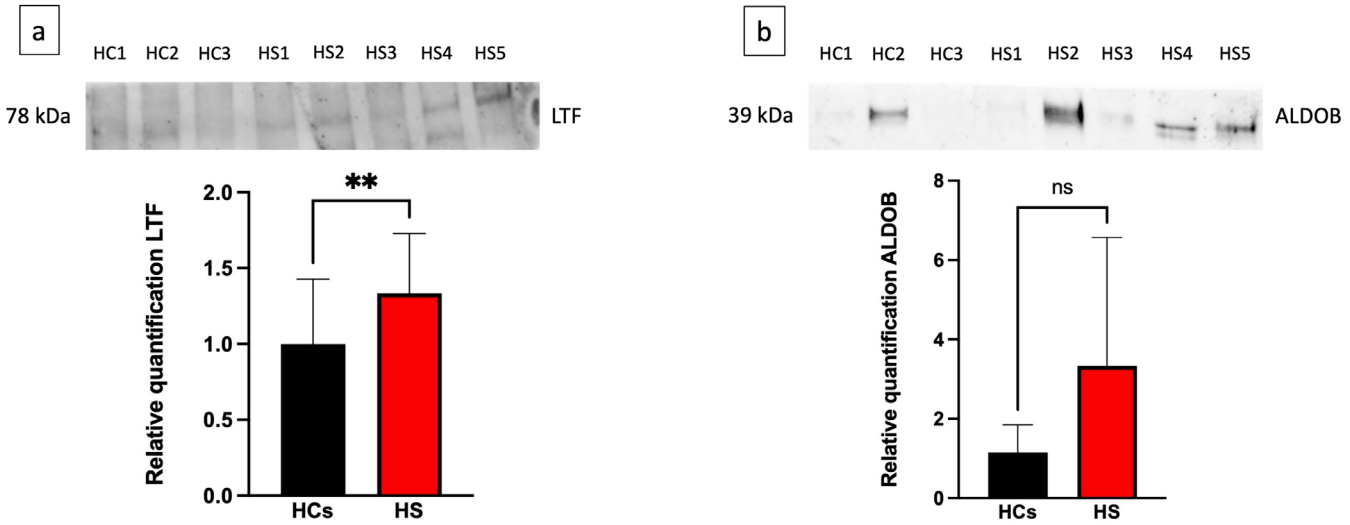


FIGURE 4 | Orthogonal validation. (a) Quantification of LTF and (b) ALDOB normalised to total protein profile in the serum of HS patients ($n = 12$) compared to healthy controls (HCs, $n = 11$). **Statistical significance was assessed using the non-parametric Mann–Whitney U test ($p = 0.0062$, ns: not significant).

neutrophil recruitment may represent rational intervention strategies [21]. Second, a keratinisation/barrier dysfunction axis, encompassing epidermal differentiation and cornified envelope pathways, was identified in our discovery-based analysis. While the directional trend observed for ALDOB supports this signature, further validation is required to confirm whether restoring barrier integrity or normalising keratinocyte differentiation could modify early pathogenic events [19, 20]. Third, an ECM remodelling/fibrosis axis, reflected by enrichment of ECM components and supported by prior evidence of MMP-driven matrix dysregulation, suggests that targeting protease activity or downstream profibrotic signalling could mitigate chronic structural damage [17, 18].

Further validation will be required to substantiate these candidate axes, including quantitative confirmation of pathway activation in lesional and perilesional skin, longitudinal assessment of circulating markers in relation to disease activity and treatment response and functional perturbation studies in keratinocyte or organoid HS models. Such investigations are necessary to determine whether modulation of these interconnected pathways translates into clinically meaningful therapeutic benefit.

Orthogonal validation of this dual signature was performed using WB in the same cohort. LTF protein was quantified for Innate Immunity/Neutrophil Axis. LTF is a primary marker of neutrophil degranulation and antibacterial response, both of

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which were top-enriched pathways in our study. WB analysis confirmed a statistically significant higher abundance of LTF in HS patients compared to HCs ($p = 0.0062$), providing robust support for the systemic inflammatory component of our model (Figure 4a).

ALDOB protein was quantified for the Keratinisation/Barrier Axis. In our cohort, WB analysis showed a consistent upward trend in HS patients compared to HCs ($p = 0.17$). While this trend aligns with the 'keratinisation and epidermal differentiation' signatures identified by MS, it did not reach statistical significance in this validation set (Figure 4b). Consequently, while the inflammatory axis is robustly confirmed, the metabolic and barrier-related findings remain at a discovery level and require further investigation.

5 | Conclusions and Perspectives

The present study should be interpreted as an exploratory, hypothesis-generating investigation. The cohort size was limited (12 patients with moderate-to-severe HS and 11 healthy controls). Although the strict selection criteria and clinical homogeneity strengthen internal validity and reduce confounding variability, the relatively small sample size constrains statistical power, limits generalisability and precludes definitive biomarker validation or robust comparative analyses with other inflammatory skin diseases. Based on a priori power estimation, the study is adequately powered to detect only large effect sizes (standardised difference ≥ 1.17), whereas smaller or moderate molecular differences may not have been reliably captured. Therefore, independent validation in larger and disease-controlled cohorts will be necessary to confirm the specificity and reproducibility of the identified proteomic alterations.

Despite these limitations, our findings identify a candidate dual molecular signature characterised by the concomitant dysregulation of keratinisation-related pathways and enhanced innate immune responses. This epithelial-immune dichotomy reinforces the concept of HS as an autoinflammatory keratinisation disorder and may have therapeutic implications. Specifically, it supports a model in which effective treatment strategies may need to simultaneously target epithelial barrier dysfunction and aberrant immune activation to achieve more comprehensive disease control. While the inflammatory component of this signature is robustly supported by our validation data, the epithelial axis represents a promising discovery that warrants further investigation in larger, independent cohorts.

Author Contributions

Conceptualisation: C.M., S.C. and P.M.T. Data Curation: C.M., S.R., S.C. and P.M.T. Formal Analysis: B.U., E.S. and R.M. Funding Acquisition: A.V.M. and P.M.T. Investigation: C.M., S.R., B.U. and P.M.T. Methodology: S.R., B.U. and E.S. Project Administration: S.C. and P.M.T. Resources: C.M., A.V.M., S.C. and P.M.T. Software: B.U., E.S. and R.M. Supervision: A.V.M., S.C. and P.M.T. Validation: C.M., S.C. and P.M.T. Visualisation: S.C. and P.M.T. Writing – Original Draft Preparation: C.M., S.R., E.M.N. and P.M.T. Writing – Review and Editing C.M., S.R., E.M.N., S.C. and P.M.T.

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Ethics Statement

The study protocol was approved by the Area B Milan Ethics Committee (protocol no. 487_2020).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in ProteomeXchange Consortium at http://www.ebi.ac.uk/pride, reference number PXD074024.

References

1. C. H. Cotton, S. X. Chen, S. H. Hussain, I. Lara-Corrales, and A. L. Zaenglein, "Hidradenitis Suppurativa in Pediatric Patients," *Pediatrics* 151, no. 5 (2023): e2022061049, https://doi.org/10.1542/peds.2022-06.

2. K. R. van Straalen, E. P. Prens, and J. E. Gudjonsson, "Insights Into Hidradenitis Suppurativa," *Journal of Allergy and Clinical Immunology* 149, no. 4 (2022): 1150–1161, https://doi.org/10.1016/j.jaci.2022.02.003.

3. R. Sabat, A. Alavi, K. Wolk, et al., "Hidradenitis Suppurativa," *Lancet* 405, no. 10476 (2025): 420–438, https://doi.org/10.1016/S0140-6736(24)02475-9.

4. K. R. van Straalen, E. P. Prens, G. Willemsen, D. I. Boomsma, and H. H. van der Zee, "Contribution of Genetics to the Susceptibility to Hidradenitis Suppurativa in a Large, Cross-Sectional Dutch Twin Cohort," *JAMA Dermatology* 156, no. 12 (2020): 1359–1362, https://doi.org/10.1001/jamadermatol.2020.3630.

5. C. Moltrasio, P. M. Tricarico, M. Romagnuolo, A. V. Marzano, and S. Crovella, "Hidradenitis Suppurativa: A Perspective on Genetic Factors Involved in the Disease," *Biomedicine* 10, no. 8 (2022): 2039, https://doi.org/10.3390/biomedicines10082039.

6. C. Moltrasio, R. Moura, A. Conti, et al., "Polygenic Score: A Tool for Evaluating the Genetic Background of Sporadic Hidradenitis Suppurativa," *Journal of Investigative Dermatology* 145, no. 8 (2025): 1987–1994, https://doi.org/10.1016/j.jid.2024.11.019.

7. Q. Sun, K. A. Broadaway, S. N. Edmiston, et al., "Genetic Variants Associated With Hidradenitis Suppurativa," *JAMA Dermatology* 159, no. 9 (2023): 930–938, https://doi.org/10.1001/jamadermatol.2023.221.

8. R. Kjærsgaard Andersen, L. Stefansdottir, P. T. Riis, et al., "A Genome-Wide Association Meta-Analysis Links Hidradenitis Suppurativa to Common and Rare Sequence Variants Causing Disruption of the Notch and Wnt/β-Catenin Signaling Pathways," *Journal of the American Academy of Dermatology* 92, no. 4 (2025): 761–772, https://doi.org/10.1016/j.jaad.2024.11.050.

9. A. S. L. E. de Oliveira, G. Bloise, C. Moltrasio, et al., "Transcriptome Meta-Analysis Confirms the Hidradenitis Suppurativa Pathogenic Triad: Upregulated Inflammation, Altered Epithelial Organization,

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and Dysregulated Metabolic Signaling," *Biomolecules* 12, no. 10 (2022): 1371, https://doi.org/10.3390/biom12101371.

10. J. Spiteri, D. Mintoff, L. Grech, and N. P. Pace, "Transcriptomic Signatures and Molecular Pathways in Hidradenitis Suppurativa-A Narrative Review," *International Journal of Molecular Sciences* 26, no. 16 (2025): 7704, https://doi.org/10.3390/ijms26167704.

11. H. J. Hurley, "Axillary Hyperhidrosis, Apocrine Bromhidrosis, Hidradenitis Suppurativa, and Familial Benign 8 Pemphigus: Surgical Approach," in *Dermatologic Surgery*, ed. R. K. Roenigk and H. H. Roenigk (Marcel Dekker, 1989), 729–739.

12. C. C. Zouboulis, T. Tzellos, A. Kyrgidis, et al., "Development and Validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a Novel Dynamic Scoring System to Assess HS Severity," *British Journal of Dermatology* 177, no. 5 (2017): 1401–1409, https://doi.org/10.1111/bjd.15748.

13. M. P. Kashyap, J. Khan, R. Sinha, et al., "Advances in Molecular Pathogenesis of Hidradenitis Suppurativa: Dysregulated Keratins and ECM Signaling," *Seminars in Cell & Developmental Biology* 128 (2022): 120–129, https://doi.org/10.1016/j.semcdb.2022.01.006.

14. J. Li, S. Li, Q. Zhang, et al., "Apocrine Gland Damage and the Release of Specific Keratins in Early Stage Indicate the Crucial Involvement of Apocrine Glands in Hidradenitis Suppurativa," *Journal of Investigative Dermatology* 145, no. 6 (2025): 1371–1384.e7, https://doi.org/10.1016/j.jid.2024.09.021.

15. H. B. Naik, J. H. Jo, M. Paul, and H. H. Kong, "Skin Microbiota Perturbations Are Distinct and Disease Severity-Dependent in Hidradenitis Suppurativa," *Journal of Investigative Dermatology* 140, no. 4 (2020): 922–925.e3, https://doi.org/10.1016/j.jid.2019.08.445.

16. P. M. Tricarico, R. Gratton, C. A. Dos Santos-Silva, et al., "A Rare Loss-Of-Function Genetic Mutation Suggest a Role of Dermcidin Deficiency in Hidradenitis Suppurativa Pathogenesis," *Frontiers in Immunology* 13 (2022): 1060547, https://doi.org/10.3389/fimmu.2022.1060547.

17. J. Sanchez, S. Le Jan, C. Muller, et al., "Matrix Remodelling and MMP Expression/Activation Are Associated With Hidradenitis Suppurativa Skin Inflammation," *Experimental Dermatology* 28, no. 5 (2019): 593–600, https://doi.org/10.1111/exd.13919.

18. N. Vecin, N. C. Balukoff, M. Yaghi, et al., "Hidradenitis Suppurativa Tunnels: Unveiling a Unique Disease Entity," *ID Innovations: Skin Science From Molecules to Population Health* 5, no. 3 (2025): 100350, https://doi.org/10.1016/j.xjidi.2025.100350.

19. C. Del Vecchio, R. Gratton, C. Nait-Meddour, et al., "Dysregulation of Aquaporin-3 and Glyceryl Glucoside Restoring Action in Hidradenitis Suppurativa In Vitro Models," *Cellular Physiology and Biochemistry* 58, no. 4 (2024): 404–417, https://doi.org/10.33594/000000720.

20. M. Akiyama, "Diseases Categorized as Autoinflammatory Keratinization Diseases (AiKDs), and Their Pathologies and Treatments," *Nagoya Journal of Medical Science* 86, no. 1 (2024): 1–15, https://doi.org/10.18999/nagjms.86.1.1.

21. L. A. C. Brandão, R. R. Moura, A. V. Marzano, C. Moltrasio, P. M. Tricarico, and S. Crovella, "Variant Enrichment Analysis to Explore Pathways Functionality in Complex Autoinflammatory Skin Disorders Through Whole Exome Sequencing Analysis," *International Journal of Molecular Sciences* 23, no. 4 (2022): 2278, https://doi.org/10.3390/ijms23042278.

22. S. L. Schell, Z. Cong, M. L. Sennett, et al., "Keratinocytes and Immune Cells in the Epidermis Are Key Drivers of Inflammation in Hidradenitis Suppurativa Providing a Rationale for Novel Topical Therapies," *British Journal of Dermatology* 188, no. 3 (2023): 407–419, https://doi.org/10.1093/bjd/ljac096.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Complete list of Differentially Abundant Proteins (DAPs) in HS patients compared to healthy controls. The table includes 306 proteins identified using a threshold of FDR adjusted q value <0.10 and fold change >1.50 or <0.667. For each protein, the gene name, UniProt ID, fold change (HS/HC), log2 fold change and both nominal p-values and BH-adjusted q-values are provided. **Table S2:** Sensitivity analysis of DAPs at a higher statistical stringency. This table lists the 194 proteins that remain significant at a more restrictive threshold of FDR adjusted q value <0.05 and fold change >1.50 or <0.667. The table includes protein identifiers, median abundance values for HS and HC groups and the median difference for each candidate.

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