




An Atlas of the Hidradenitis Suppurativa Transcriptome

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ABSTRACT

Introduction: Hidradenitis suppurativa (HS) is a chronic inflammatory condition of the skin. Both genetic and environmental factors contribute to the risk of developing HS, but the pathogenesis of this disease is currently not fully understood. The aim of this study was to further current understanding of the molecular background of HS with the use of global transcriptome analyses.

Methods: Transcriptome profiling of perilesional and lesional skin of five patients with HS and six healthy control patients was performed by next-generation sequencing. Groups of

differentially expressed genes characteristic of the skin of patients with HS were shortlisted by bioinformatic analysis.

Results: RNA sequencing followed by bioinformatic profiling revealed profound enrichment of inflammatory-related processes in both lesional and perilesional skin of patients with HS. There were, however, distinct differences in the gene expression profiles between the lesional and perilesional skin, with 1488 genes differentially expressed. Genes encoding typical proinflammatory cytokines were profoundly enriched within HS lesions. In contrast, those encoding mediators of extracellular matrix organization were highly expressed mostly in the perilesional area.

Conclusions: Our study provides novel insights into the mechanisms underlying the pathogenesis of HS, and the results also have poten-

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tial clinical implications in both diagnosis and therapeutics.

Keywords: Hidradenitis suppurativa; Transcriptome; Matrix remodeling; Inflammation

Key Summary Points

Why carry out this study?

Both genetic and environmental factors contribute to the risk of developing hidradenitis suppurativa (HS), but the pathogenesis of this disease is currently not fully understood.

What was learned from the study?

Global transcriptome analysis of lesional and perilesional skin of patients with HS identified numerous differentially expressed genes that displayed unique expression patterns in HS.

The expressions of several genes identified in the analysis were dysregulated in the skin of patients suffering from HS and are novel biomarker candidates and potential putative therapeutic targets for HS.

Our study provides novel insights into the mechanisms underlying the pathogenesis of HS, and the results have potential clinical implications in both diagnosis and therapeutics.

INTRODUCTION

Hidradenitis suppurativa (HS) is a prevalent inflammatory dermatosis with a well-documented, devastating effect on patients' quality of life [1, 2]. This dermatological condition is characterized by the formation of deeply seated inflammatory nodules, abscesses, inflammatory tunnels, and vast scarring in the intertriginous areas, including armpits, groins, anogenital zone, and buttocks [2]. The pathogenesis of HS is complex and yet to be fully understood;

however, recent studies indicate possible genetic implications of the disease [2–8]. There are three phenotypes of HS: sporadic, familial, and syndromic, with overlaps possibly present. Each type is characterized by genetic variation [9]. A positive family history for HS has been reported in almost 30% of cases [3, 10]; also mutations in genes encoding γ -secretase, mainly those impairing or decreasing its function, may play a role in the development of familial HS [5, 6]. However, to the best of our knowledge, the majority of patients with a family history of HS do not harbor this mutation. Mutations in genes related to autoinflammation and immune response, including MEFV and NOD2, have also been described in the familial HS [11, 12]. Despite this knowledge, the exact genetic implications of the disease still remain unresolved.

The concept of personalized medicine—i.e., treatment tailored for the specific patient—is one of the most significant milestones of modern medicine [13]. This concept is based on the principle that the underlying heterogeneity of diseases in patients is so essential that the treatment should be personalized for every individual, depending on their biochemical, behavioral, environmental exposure, and psychological profile [14]. The advances and applications of new, emerging biomedical assays, including RNA sequencing, have led to the discovery of various interactions that may be significant in terms of disease course [13]. We hypothesized that this concept might also apply to HS, the course and clinical manifestations of which are highly heterogeneous [15]. Therefore, we conducted an RNA sequencing study on the lesional and perilesional skin of patients suffering from HS and compared the results with those from the skin of healthy controls. In a previous study, we demonstrated that perilesional skin did not show any signs of inflammatory reactions [16].

MATERIALS AND METHODS

Patients

The study was performed on skin biopsy material collected from five patients with HS who underwent surgical excision of skin lesions in the Department of Dermatology, Venereology, and Allergology, Wrocław Medical University, between June and November 2022. All patients were examined by a dermatologist with experience treating patients with HS. The study group consisted of three women and two men (60% and 40% of study population, respectively). The mean (\pm standard deviation [SD]) age of the patients was 35.2 ± 12.0 years, and all were considered to be obese (mean body mass index [BMI] 31.8 ± 7.3). The mean duration of HS was assessed as 9.4 ± 5.9 years. The mean International Hidradenitis Suppurativa Severity Score System (IHS4) score was 20.2 ± 8.4 , indicating severe disease. Three patients were assessed at Hurley stage 2 and two patients at Hurley stage 3. The majority of subjects ($n = 3$, 60%) were active smokers, with a mean of 9.8 ± 1.8 pack-years. Only one patient (20%) reported having a positive family history of HS, while two patients (40%) reported suffering from juvenile acne. Demographic details on the study group are presented in Table 1.

Additionally, skin samples from six healthy controls (HCs) were collected from the age- and sex-matched patients who underwent a surgical procedure for non-malignant skin lesions localized on the trunk.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Wrocław Medical University (KB-779/2022 and KB-520/2018). All patients signed informed consent before entering the study.

Biopsy

Before the procedure, the biopsied area was marked by the dermatologist who performed the biopsy. Subsequently, the subjects were injected with a mixture of anesthetic (2% lidocaine) and adrenaline to diminish the

Table 1 Demographics of study group

Characteristics	Patients ($n = 5$)
<i>Sex, n (%)</i>	
Males	2 (40%)
Females	3 (60%)
<i>Age, years (mean \pm SD)</i>	
	35.2 ± 12.0
<i>Body mass index (BMI), kg/m² (mean \pm SD)</i>	
	31.8 ± 7.3
<i>Smoking</i>	
Number of patients who smoked (%)	3 (60%)
Pack-years (mean \pm SD)	9.8 ± 1.8
<i>Positive for family history of HS, n</i>	
	1 (20%)
<i>Age at the onset, years (mean \pm SD)</i>	
	25.8 ± 13.6
<i>HS duration, years (mean \pm SD)</i>	
	9.4 ± 6.6
<i>Hurley staging, n</i>	
Hurley stage 1	0
Hurley stage 2	3 (60%)
Hurley stage 3	2 (40%)
<i>IHS4, points (mean \pm SD)</i>	
	20.2 ± 8.4
<i>Previous treatment, n (%)</i>	
Antibiotic	4 (80%)
Biologics	0
Retinoids	1 (20%)
Surgery	1 (20%)
<i>Operated area, n (%)</i>	
Armpit	5 (100%)
Groin	0
Submammary area	0

BMI Body mass index, *IHS4* International Hidradenitis Suppurativa Severity Score System, *SD* standard deviation

procedural pain and impede bleeding. Two 5-mm punch biopsies were taken from the marked area: one from the active, inflammatory nodule and the second from the healthy-

looking skin near the selected lesion (at least 2 cm in diameter). At the time of the biopsy, the patient had not been receiving any anti-inflammatory medication.

RNA Isolation

All collected skin samples were frozen in RNA-later (Sigma-Aldrich, St. Louis, MO, USA) and stored at -80°C until analysis. For total RNA isolation, the samples were homogenized in Fenzol (A&A Biotechnology, Gdansk, Poland) using a tissue homogenizer (OMNI International, Kennesaw, GA, USA).

RNA Sequencing

Messenger RNA (mRNA) Sequencing (RNA-Seq) libraries were prepared with the Ion AmpliSeq™ Transcriptome Human Gene Expression Kit (Thermo Fisher Scientific, Waltham, MA, USA). Sequencing was conducted on Ion Proton system (Thermo Fisher Scientific). Reads were aligned to the hg19 AmpliSeq Transcriptome ERCC v1 with Torrent Mapping Alignment Program and processed with the RNASEQ Analysis pipeline (version 5.0.4; Thermo Fisher Scientific). Transcripts were quantified with HTseq-count (version 0.6.0) with default options [17]. Differential gene expression was established with DESeq2 (version 1.18.1) [18]. The RNA-Seq data are available at the Gene Expression Omnibus repository (<https://www.ncbi.nlm.nih.gov/geo/>) under the entry GSE245451.

Functional Analysis of RNA-seq

Functional gene ontology enrichment analysis of differentially expressed genes (DEGs) (fold change > 1.5 and adjusted p -value [adj.- p] < 0.05) was performed using the R package clusterProfiler version 4.4. [19, 20]. Gene lists were searched using the Ensembl gene annotation (ENSEMBL_GENE_ID) with the *Homo sapiens* background dataset used for analyses [21]. Volcano plots and dot plots were created using the ggplot2 libraries in R (R Foundation for Statistical Computing, Vienna, Austria). Venn

diagrams were designed using the free online available tool (<http://bioinformatics.psb.ugent.be/webtools/Venn>). Heatmaps were constructed using the GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

RNA-Seq Analysis of Skin Biopsies from HS Patients and Control Subjects

Total RNA was extracted from the skin biopsies of lesional skin of patients with HS (HS skin; $n = 5$ patients), non-lesional (perilesional) skin of the same five patients with HS (2 cm distant from the skin lesion; periHS skin; $n = 5$ patients), and normal skin from HCs (Control skin; $n = 6$ patients) (Fig. 1a). High-throughput RNA-Seq analysis was then used to profile transcriptome changes in the skin of patients with HS. Principal component analysis (PCA) illustrated distinct clustering of the HS, periHS, and HC skin samples (Fig. 1b). We identified a plethora of DEGs based on the three comparisons: HS versus Control, periHS versus Control, and HS versus periHS (Fig. 1c). The greatest difference was observed for the comparison of lesional (HS) and HC (Control) skin (1906 downregulated and 3107 upregulated DEGs with fold change cutoff of > 1.5 and adj.- $p < 0.05$ in HS relative to Control). Interestingly, the perilesional skin (periHS) also showed remarkable changes in the gene expression profiles. Compared to the Control, there were 400 downregulated and 525 upregulated genes in the HS and periHS skin samples. Additionally, a comparison of the lesional (HS) and perilesional skin (periHS) samples indicated a substantially larger number of genes showing a consistent difference in expression in the HS skin (444 down- and 1044 upregulated genes).

Comparative Transcriptomics Reveals Unique Potential of HS Susceptibility Genes

A Venn diagram was plotted to compare statistically upregulated DEGs in all comparisons: HS

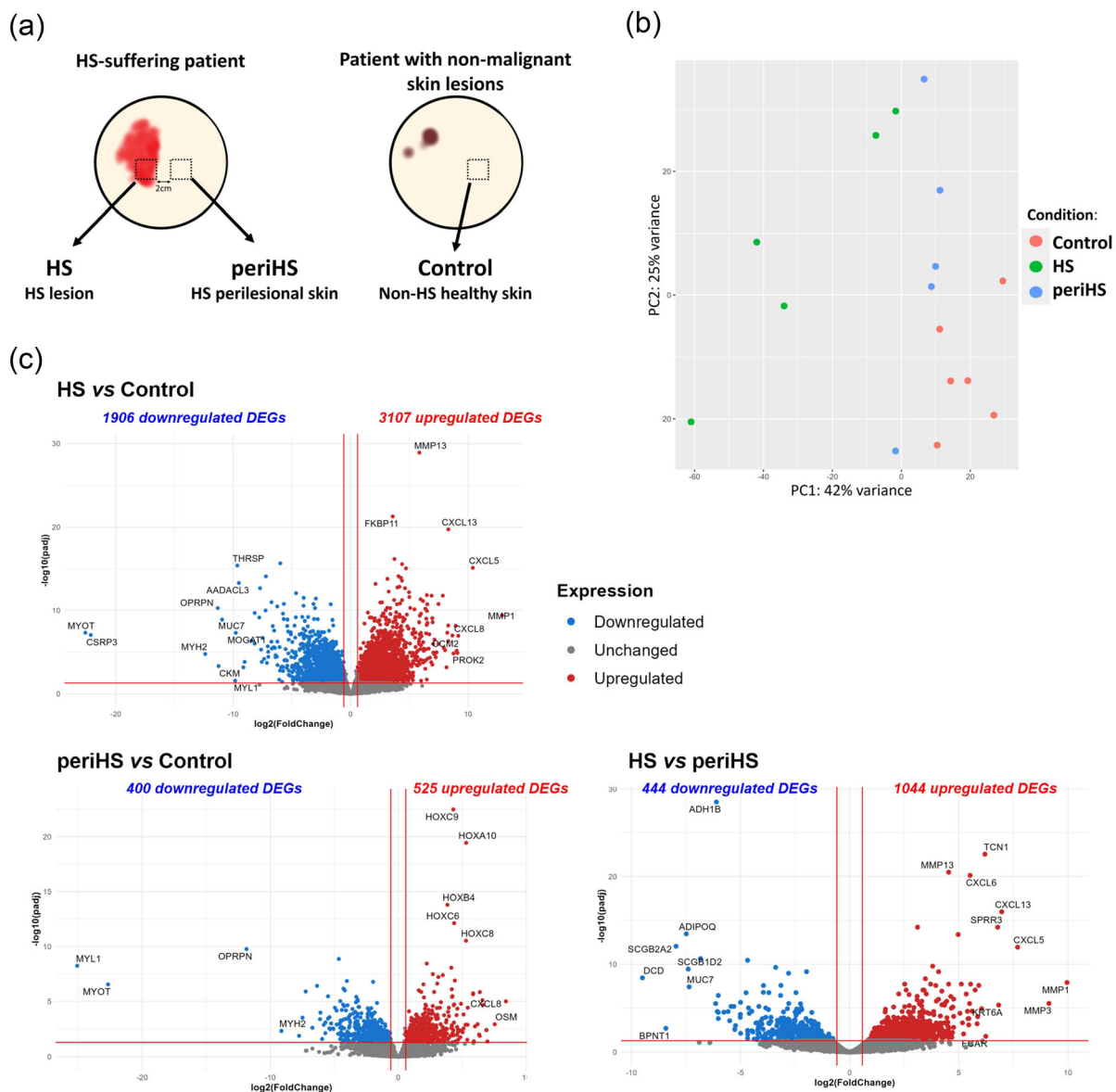


Fig. 1 RNA-sequencing (RNA-Seq) analysis. **a** Scheme showing patient materials collected for RNA-Seq analysis. **b** Principal component analysis (PCA) plot of RNA-Seq dataset. **c** Volcano plots representing differentially expressed genes (DEGs) between all comparisons.

Criteria for DEGs: adjusted p -value < 0.05, fold change > 1.5. *Control* Skin from normal, healthy control (HC) subjects, *HS* lesional skin of patients with hidradenitis suppurativa, *periHS* non-lesional skin of patients with HS at 2 cm distant from the skin lesion

versus Control, periHS versus Control and HS versus periHS (Fig. 2a). Consistently, 434 DEGs were upregulated in both lesional (HS) and perilesional skin (periHS) ((HS + periHS)) compared to the Control. We identified 337 genes that were not differentially expressed between the periHS and HS groups, whereas 95 were

upregulated in the HS skin compared to the periHS skin. In addition, we identified 754 DEGs as specific for lesional skin (HS) only, compared to both perilesional and control (HC) skin. Using a similar approach, we found that 21 DEGs were unique for periHS skin. An

analogous analysis was conducted for the downregulated DEGs (Fig. 2b).

Gene Expression Profile Analyses Reveal Remarkable Enrichment of Inflammatory Pathways in Lesional and Perilesional HS Skin

We performed bioinformatic analyses of the 337 upregulated and 306 downregulated DEGs that were common to the HS and periHS groups compared to the Control (HC) group; the expression level of these DEGs did not differ between the HS and periHS (Fig. 3a, b). Accordingly, the most highly represented upregulated biological processes in this comparison were related to cell activation involved in the immune response (e.g., *CD28*, *CD63*, *CD86*, *CD96*, *CD177*, *CD180*), extracellular matrix organization (e.g., *COL4A2/A4*, *COL6A5*, *COL8A1*, *FKBP10*, *FLOT1*, *MMP2*, *SERPINH1*, and *SLC2A10*), and cell-substrate adhesion (e.g., *GREM1*, *ITGA4/5*, *ITGB1/2*, *KDR*, *LIMS1*, *PARVG*) (Fig. 3a, c). Downregulated DEGs in both HS and periHS biological processes were mostly annotated to the lipid catabolic process (e.g., *ABDH5*, *ACER1*, *CYP1A2*, *GPLD1*, *LPIN1*, *PNPLA4/5*, *PPARA*) (Fig. 3b, c).

As a next step, we performed GO analysis of the HS and periHS common genes, which were also upregulated in the HS versus periHS comparison (95 DEGs). This comparison mostly indicated genes for enhanced immune cell chemotaxis and migration (e.g. *IL1B*, *IL6*, *IL8*,

CXCL1/5, *CCL11*,) and extracellular matrix organization (*ADAMTS2/4/12*, *COL1A2*, *COL3A1*, *COL4A1*, *COL5A1/2*, *PDPN*, *PXDN*) (Fig. 4a, b).

Analysis of the HS-specific subset of 754 DEGs that were only upregulated in HS revealed an array of functions that involve migration of leukocytes, granulocyte and myeloid cells, response to bacteria and lipopolysaccharide, and activation of T and B cells (Fig. 5a). DEGs with elevated expression in HS skin compared to periHS or Control skin were significantly enriched with genes associated with immune response, such as, for example, *CCL3/4/5/18/24*, *CXCL2/3/6/10/13*, *IL17A/F*, *S100A7/8/9*, and *IL1A* (Fig. 5b). Conversely, 292 downregulated genes were annotated to a range of biological processes, including lipid metabolic process (e.g. *ABCA3*, *ABHD6*, *ADIPOQ*, *APOD*, *PDK14*, *PPARG*, *RORA*, *SERPINA12*, *WNT4*) and epidermis development (e.g. *EDAR*, *FGF10*, *KRT7/15/31/77*, *LCE1B/C*, *TGM5*) (Fig. 5b, c).

DISCUSSION

The underlying pathogenetic mechanisms involved in the development of HS remain unexplained. Genetic predisposition, obesity, and smoking seem to drive a vicious inflammatory cycle, leading to the creation of skin lesions and, consequently, tissue destruction [1]. Many studies have been performed, resulting in the identification of multiple inflammatory pathways involved in HS, including the

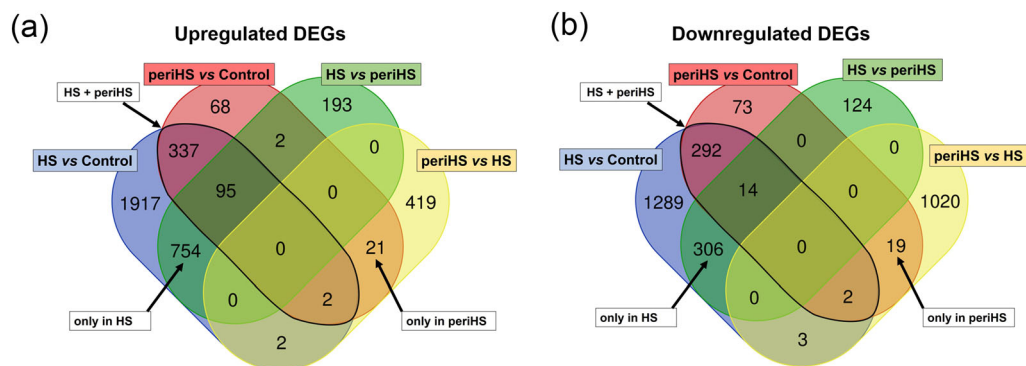


Fig. 2 a, b Venn diagram presenting comparison of upregulated (a) and downregulated (b) DEGs in lesional skin (HS) versus healthy skin (Control), perilesional skin (periHS) versus Control, HS versus periHS and periHS versus HS

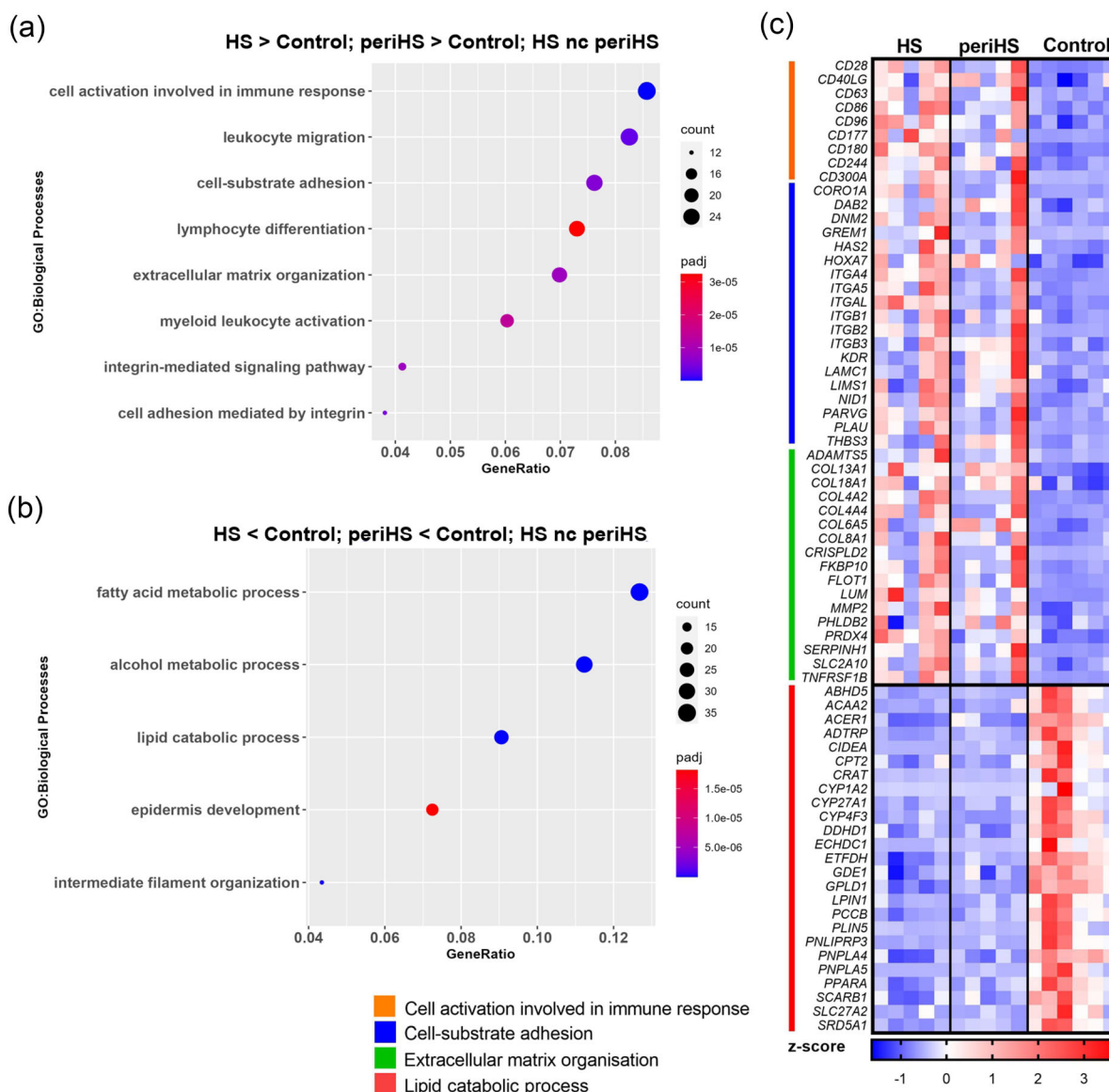


Fig. 3 Functional gene analysis of DEGs common to the HS and periHS skin. **a, b** Gene Ontology (GO) enrichment analysis of upregulated (**a**) and downregulated (**b**) biological processes common to the HS lesional (HS) and perilesional (periHS) skin compared to skin of healthy patient (Control), with no difference between the HS and periHS skin. The color and size of each bubble represent

the enrichment significance (adjusted p -value [$adjp$]) and number of genes enriched in each GO term ($count$), respectively. **c** Heatmap illustrating the expression levels (Z score) of up- and downregulated DEGs selected from the GO enrichment analysis. ‘>’ Upregulated, ‘<’ — downregulated, nc not changed

interleukin (IL)-23/IL-17 pathway, dendritic cells, neutrophil tissue infiltration, and development of neutrophil extracellular traps [22–27]. The production of IL-1 in fibroblast and keratinocytes, complement activation, and skin

microbiome disturbances have also been described [28–30]. Although the distinct contribution of T cells to the development of inflammatory milieu in HS has been emphasized, the results of the study by Sabat et al. [31]

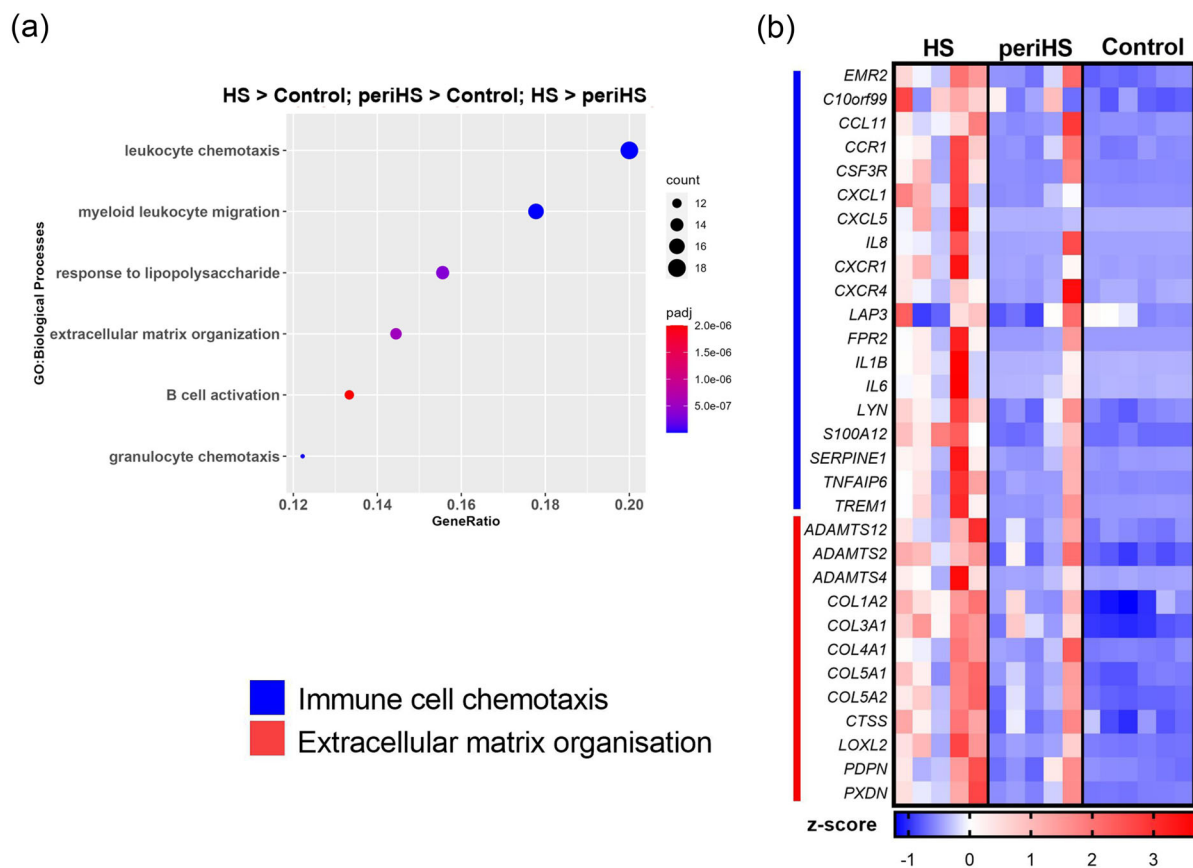


Fig. 4 Functional gene analysis of DEGs common to the HS and periHS skin, but upregulated in the HS versus periHS comparison. **a** GO enrichment analysis of upregulated biological processes common for HS lesional (HS) and perilesional (periHS) skin compared to skin of healthy

patient (Control). **b** Heatmap illustrating the expression levels (Z score) of up- and downregulated DEGs selected from the GO enrichment analysis. ‘>’ Upregulated, ‘<’—downregulated

have proven B and plasma cell persistence and function in HS lesions. In their study, both B and plasma cells and B-cell activating factor (BAFF) were abundant in HS lesions, particularly in inflammatory nodules and abscesses [31]. In the presence of bacterial products, granulocyte colony-stimulating factors stimulated neutrophils to secrete BAFF. The characterization of the pathway revealed its involvement in the multiple functions of B/plasma cells, including their migration, proliferation, survival, and activation [31]. It is worth underlining that there has been a shift in the understanding of HS lesions as a source of inflammation. While scarring tissues and non-draining tunnels are primarily considered to be static lesions that did

not influence the further deterioration of the tissue [32], the genetic, epigenetic, and cytokine profile of HS tunnels, as well as the influence of the presence of proinflammatory gelatinous mass and microbiota, highlights their possible implications in further skin deterioration due to the disease.

Interestingly, studies have shown that the inflammation associated with HS extends to the healthy-looking perilesional skin [24, 33]. The authors of these two studies described enhanced mRNA of IL17A, IL17C, and IL1 β in both perilesional and affected skin of patients with HS. Also, a group led by Navrazhina [34] observed the upregulation of several immune axes, like T_H1, T_H2, T_H17, and T_H22, both in lesional and

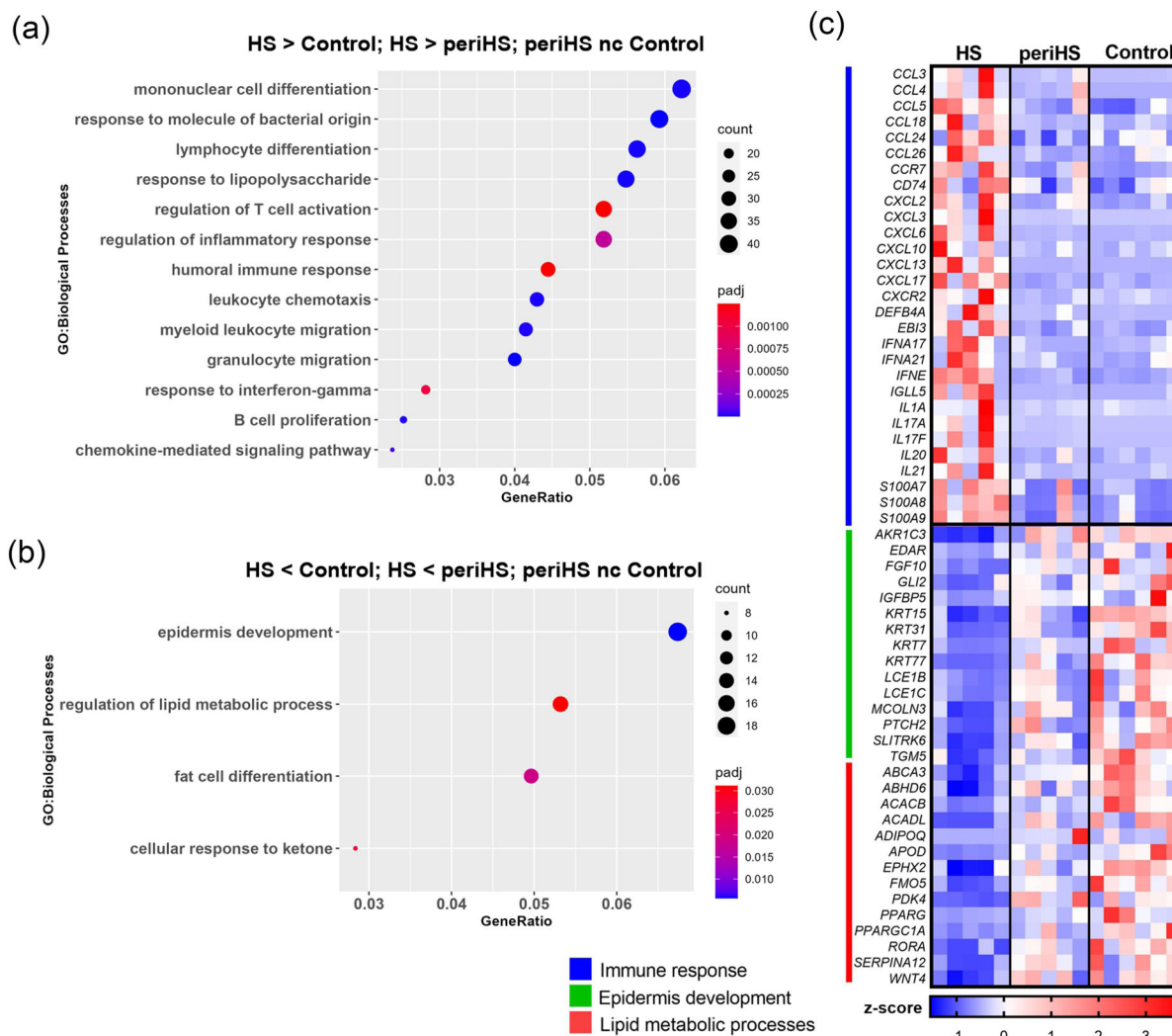


Fig. 5 Functional gene analysis of DEGs unique for HS lesional skin. **a**, **b** GO enrichment analysis of up- (**a**) and downregulated (**b**) biological processes in HS lesional (HS) skin compared to periHS and control skin. **c** Heatmap illustrating the expression levels (*z* score) of up- and

downregulated DEGs selected from the GO enrichment analysis. ‘>’ Upregulated, ‘<’ —downregulated, *nc* not changed

perilesional skin. These authors found a similar enrichment of genes having a role in the neutrophil chemotaxis, migration, and extravasation in lesions and perilesional skin (among others those encoding IL1- β , CXCL1-3, MDK, CD177) in comparison to healthy controls [34].

In contrast to the above reports, our previous study did not indicate an enhanced inflammatory influx into the perilesional skin but only into the HS lesion [16]. One of the possible reasons for this discrepancy may relate to the

ethnic diversity of patients participating in the studies. Genetic, epigenetic, and/or environmental factors have been previously been described as the key contributors to the severity of HS [3].

In the present study, despite the lack of apparent inflammatory reaction in the perilesional area, on the molecular level, both lesional and perilesional HS skin demonstrated a profound upregulation of inflammatory-related genes functionally assigned mostly to the

activation, proliferation, and differentiation of immune cells but not to typical proinflammatory cytokines or chemokines. As expected, profound differences in the gene expression profile between lesional and perilesional HS skin were observed, and these differences mainly reflected ongoing the HS-specific inflammatory process. The most significantly upregulated DEGs in lesional skin encode cytokines, chemokines and other mediators related to the chemotaxis/migration of granulocytes and response to bacteria molecules.

In addition, the dysregulated expression profile of genes encoding key components of extracellular matrix (ECM) was observed already in the periHS but not within HS lesion itself. The ECM proteins are important regulators of epidermal homeostasis, ensuring the proper balance of keratinocyte proliferation and differentiation. Dysregulation of ECM composition is a hallmark of many skin pathologies of inflammatory background and has already been documented in HS [35, 36]. Shortlisted DEGs, which already show high expression profiles in perilesional skin, could thus be selected as candidate biomarker genes in subsequent studies.

There are a number of limitations to our study. Firstly, our study involved only five patients and six healthy controls. Although the sample size may seem small, according to the available data [37], RNA-Seq studies may be performed when the sample size is $n = 3$ in each group. Secondly, we included only patients from one center, which may have caused bias in the over-expressed DEGs. Future studies with a higher diversity of subjects may positively influence the generalizability of the results.

Our study significantly expands current knowledge on the molecular basis of HS. In contrast to the study by Navrazhina et al. [34], we identified distinct groups of genes whose expression was significantly modulated in the lesional skin only. Taken together, our study provides novel insights into the mechanism driving the pathogenesis of HS. Identification of differentially expressed genes that are unique to HS lesions may have valuable clinical implications for both the diagnosis of HS and for developing new targeted therapies.

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Author Contribution. All authors assisted in the concept and design, drafting, editing, and revisions of this manuscript.

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Data Availability. Sequencing data have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE245451. Any additional data are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. The authors declare they have no conflicts of interest.

Ethical approval. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Wrocław Medical University (KB-779/2022 and KB-520/2018). All patients signed informed consent before entering the study.

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