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REVIEW ARTICLE OPEN ACCESS

The Multifaceted Role of Keratinocytes in Hidradenitis Suppurativa Pathogenesis

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Received: 19 November 2025 | **Revised:** 29 April 2026 | **Accepted:** 4 May 2026

Keywords: dermal tunnels keratinocytes | epithelial keratinocytes | hidradenitis suppurativa | inflammation | keratinocytes | pathogenesis

ABSTRACT

Hidradenitis suppurativa (HS) is a chronic autoinflammatory skin disorder of the pilosebaceous unit, with multiple factors contributing to its onset, activity and progression. Alongside a predisposing genetic background, hormonal and microbiome alterations, dysregulation of innate and adaptive immune response, as well as environmental/epigenetic factors contribute to its immunopathogenic landscape. In the past years, translational investigations identified several distinct inflammatory networks, not only in the chronic but also in the early stages of disease, making them potential therapeutic targets. Emerging evidence underlies the important role of keratinocytes in the pathogenesis and progression of HS, acting not only as targets of inflammatory signaling pathways but also as active producers of pro-inflammatory cytokines, chemokines and effector molecules that may influence disease onset and activity. Despite these insights, different aspects of their involvement remain underexplored, necessitating further targeted research. This review aims to highlight the experimental evidence supporting the crucial role of keratinocytes in the inflammatory response and overall pathophysiology of HS.

1 | Introduction

Hidradenitis suppurativa (HS) is a chronic-recurrent cutaneous disorder of the pilosebaceous unit, recently recognized as an autoinflammatory keratinization disease (AIKD) [1–4]. It is clinically characterized by inflammatory nodules, painful abscesses and pus-draining tunnels in intimate body areas, often accompanied by extensive scarring. The most accredited hypothesis of HS pathogenesis asserts that it is a T helper (Th)1/Th17 process, which evolves in a three-stage sequence of events: follicular hyperkeratosis, occlusion/dilatation of the terminal hair follicle, and subsequent inflammation [5]. Although still a matter of debate, recent evidence has pointed towards an aberrant inflammatory process as the key driver of HS onset and development, followed by follicular occlusion/plugging/dilatation and further downstream inflammation. In this context, 'early' HS can be considered a follicular-centred inflammatory process, although a crucial role is also played by adjacent epidermis and dermis, as shown by recent evidence [6]. This scenario can lead to recurrent deep-seated nodules and abscesses typically occurring in apocrine gland-bearing skin and associated with microbiome dysbiosis and leukocyte infiltration [7]. 'Later' HS is associated with progressive formation of epithelialized tunnels, changes in immune inflammatory infiltrate, and heavy tissue remodelling and scarring [8].

Our current understanding of HS physiopathology is mainly supported by gene expression profiling of skin biopsies, as we still lack experimental disease models that closely mimic disease phenotypes or pathophysiological processes. Previous translational investigations identified several distinct inflammatory networks, such as those including T and B cells and complement cascade as important drivers and potential druggable targets in HS [9, 10]. Despite many advances in knowledge,

our understanding of the triggering factors associated with self-perpetuating follicular/perifollicular inflammation remains incomplete.

This narrative review retraces and discusses the experimental evidence of the important contribution of keratinocytes (KCs) in HS pathophysiology.

2 | Materials and Methods

2.1 | Literature Search

A selective literature search was conducted in PubMed. The main search was performed using the following terms: 'hidradenitis suppurativa', 'acne inversa', 'keratinocytes', 'hidradenitis suppurativa pathogenesis'. Additionally, relevant keywords were used in different combinations for free-hand search and the bibliography of selected articles was reviewed. Our literature search included only experimental studies specifically investigating the structure, function and role of keratinocytes in the onset, activity and progression of HS. Articles written in the English language and published from 2004 to March 2026 were considered.

3 | Results and Discussion

Table 1 provides an overview of the main findings of the considered literature, while Figure 1 illustrates the proposed role of KCs in HS pathogenesis.

Overall, the results from our literature search showed a pleiotropic and active role of keratinocytes in HS pathogenesis across different stages of disease. Intrinsic defects in KCs differentiation may be associated with the familial form of HS (mainly caused by gamma-secretase gene mutations), while an intrinsic pro-inflammatory signature of KCs may act as a primer of inflammation in the early stages of sporadic HS. Furthermore, keratinocytes have been shown to play a key role in dermal tunnel formation and activity during the later stages of the disease.

3.1 | Early Epidermal/Follicular KC Priming

Different skin layers in HS are associated with distinct inflammatory signatures, reflecting a specific disease stage cellular composition. Epithelial keratinocytes are not only targets of inflammatory signalling pathways but also active producers of pro-inflammatory mediators, which could potentially trigger and amplify disease onset and activity.

In line with this, in early HS lesions, cultured epidermal KCs have been shown to autonomously secrete C-C Motif Chemokine Ligand (CCL) 3, C-X-C Motif Chemokine Ligand (CXCL) 3, and interleukin (IL)-8, which are known to promote the recruitment of distinct immune cells, including neutrophils, CD8+ T cells and natural killer (NK) cells, to the epidermis. In the presence of interferon (IFN)-γ, which is dependent on immune cell infiltrate in vivo, cultured KCs also express increased levels of IL-1β, IL-12, IL-23 and IL-36γ. In this context, the close interaction between KCs and immune cells is associated with a broad inflammatory profile, establishing an early environment capable of driving HS lesions progression [29]. Interestingly, IL-1β, together with interferon γ-induced protein 10 kDa (IP-10) and CCL5, is also secreted by KCs isolated from hair follicles of HS patients, either constitutively or upon pattern recognition receptor stimulations, suggesting a functional defect of KCs that may lead to a balance prone to inflammatory response [13, 37]. The confirmed overexpression of IL-1β in HS epidermis, in an NLRP3 inflammasome-dependent manner, is able to promote a massive influx of IL-17-expressing neutrophils, thus exacerbating an inflammatory loop. In the same context, IL-17-producing cells potentially contribute to the initiation of cutaneous inflammation in both HS lesional and perilesional skin [14, 19]. Of note, Daijnoki et al. [25] reported an already overexpression of IL-1β, IL-23 and TNF-α in non-lesional HS epidermal skin in the absence of further significant increase at the lesional epidermal level. Considering that during disease progression, inflammatory cells and T helper (Th)1/Th17-related mediators' production is significantly pronounced in lesional dermis, the authors speculate that KCs could act as key driver cells in the HS pathogenic scenario, favoring the switch of non-inflammatory Th17 cells into dermal inflammatory cells. According to the same study [25], immunohistochemistry analysis revealed that KCs activity in HS non-lesional skin is prominent in both interfollicular and follicular epidermis; this observation confirms previous findings indicating that a dysregulated immune response of follicular KCs may be a potential driver of HS [21]. Noteworthy, Jin et al. [27] observed that basal progenitors give rise to pathogenic KCs clones by modulating their cell line restriction, and these clones are associated with epidermal hyperproliferation and dysregulated inflammation in HS. By reconstructing the cell differentiation trajectory and using CellChat modeling, the authors identified two KCs populations (*POSTN*/*ASS1* and *S100A* clusters) able to amplify immune responses in HS. More in detail, the KCs population more specific to HS is related to the basal/spinous transitional and early-stage spinous cluster and hallmarked by S100A7/8/9 and keratin (KRT) 6 family members that promote the release of IL-1, IL-10 and complement cascade activation. Notably, IL-1R2, an IL-1 signaling transduction inhibitor, is decreased across all HS epidermal populations, suggesting an altered monocyte and Langerhans cell trafficking in HS. At the same time, all HS KCs subpopulations show an overexpression of IL-1 signaling, confirming a pronounced priming of innate immunity. In addition, the same authors demonstrated the activation of several clinically significant inflammatory enhancers in HS basal KCs CD49f^{high}, such as the enhancer of S100A8 that plays a crucial role in regulating the local chromatin environment of target loci in HS KCs, thus highlighting an amplification of HS/KCs-related genes by epigenetic regulatory mechanisms [27].

Recently, a novel migratory S100+ pathogenic KCs state has been reported in a preprint by Du-Harpur and colleagues [35]. Basal KCs invading the dermis form inflammatory epithelial niches which co-localize with COL6A5+ papillary fibroblasts, who are responsible for the migratory and proliferative behaviour of basal KCs. This finding not only suggests that this interaction could play a role in the progression of HS but also reflects the evolutionary origin of the pilosebaceous unit, since

TABLE 1 | An overview and the main results of the considered literature about the role of keratinocytes in hidradenitis suppurativa.

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Gniadecki et al. [11]	Explore the presence and abundance of lipid rafts in HS epidermis, hair follicles and sinus tracts	Observational human tissue data	HS lesional and perilesional skin ($n=5$); HCs skin ($n=4$)	Confocal laser-microscopy	Lipid rafts-enriched KCs are similar to transit-amplifying cells in lesional HS epidermis and sinus tracts Activated $CD29^{bright}CTx^{bright}$ KCs are involved in sinus tracts formation
Xiao et al. [12]	Investigate the biological pathways disrupted in KCs *NCSTN* defective	In vitro functional KCs assay	*NCSTN* knockdown HaCaT cells	CCK-8 assay; Flow cytometry; RT-PCR; Microarray analysis; WB; IHC	*NCSTN* inhibition leads to increased KCs proliferation with the majority of cells in phase S *NCSTN* knockdown results in the downregulation of Notch signalling and the upregulation of Pi3/AKT pathway
Hotz et al. [13]	Identify the pattern of inflammatory response of KCs	Observational human tissue data Ex vivo KC assay	KCs culture from hair follicle ORS cells ($n=6$)	Flow cytometry; ELISA; RT-PCR; Microarray analysis	Increased frequencies of CD4+ T cells secreting IL-17 or IL-22 + in HS patients' blood Over-expression of IP10, CCL5 and Il-1β in HS cultured KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Lima et al. [14]	Explore the localization and expression of inflammation-associated molecules	Observational human tissue data Ex vivo KC assay	34 skin biopsies from HS patients ($n = 22$) Epidermal proteins extract	IHC; WB	Up-regulated expression of NLRP3, caspase-1, S100A8/A9 in lesional HS epidermis Increased IL-17^{+} cells in HS lesional and perilesional skin Infiltrating neutrophils acted as a source of IL-17
Wolk et al. [15]	Identify and characterize the key players in HS pathogenesis.	Observational human tissue data Ex vivo KC assay	18 blood plasma and serum from HS patients ($n = 29$) Surgically excised skin areas or skin punch biopsies from HS patients ($n = 11$) Primary cells cultures	Enzyme-linked immunosorbent assay; qRT-PCR; IHC	Up-regulated LCN2 expression, with granulocytes and KCs being sources of the latter Granulocytes and KCs upregulate LCN2 expression in response to (TNF)-α LCN2 blood levels correlate with HS disease severity
Jones et al. [16]	Investigate KCs viability, migration and functions	Ex vivo KC assay	Cultured KCs from HS patients and from patients with chronic wounds; normal KCs	Cell viability and apoptosis assay; Luminex screening array	HS KCs exhibit delayed migration compared to normal KCs Reduced expression of IL-22 in HS cultured KCs No differences in cell viability and apopotosis compared to normal KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
He et al. [17]	Characterize differential miRNA expression in defective *NCSTN* cells	In vivo functional genetic study (mouse model) Observational tissue data (transcriptome)	HS lesional skin from patients with *NCSTN* mutations ($n = 5$); HCs skin ($n = 5$); $Ncstn^{\Delta KC}$ mice	mRNA sequencing; qRT-PCR; in situ hybridization; WB; luciferase reporter assay; chromatin immunoprecipitation	Donwregulation of mir-30a-3p leads to upregulation of RAB31, that in turn, accelerates EGFR degradation (with final abnormal KCs differentiation)
He et al. [18]	Explore AKT expression and activation in defective *NCSTN* cells	Observational human tissue data Functional genetic study (mouse model) In vitro KC assay	HS lesional skin from patients with *NCSTN* mutations ($n = 5$); HCs skin ($n = 5$); $Ncstn^{\Delta KC}$ mice	qRT-PCR; in situ hybridization; immunofluorescence; WB; CCK-8 assay	Downregulation of mir-100-5p leads to upregulation of p-AKT (that promotes KCs proliferation)
Marohn et al. [19] (Preprint article)	Identify cytokine expression changes in disease progression and interaction between distinct immune cells	Ex vivo human tissue study (spatial transcriptomics)	Dissected patients' tissue (epidermal and dermal regions, hair follicles, and sinus tracts)	Immunofluorescence; scRNA sequencing	KCs lining sinus tracts show increased expression of SCD1 and CEA (sebaceous and sweat-gland marker genes, respectively) HS perilesional epidermis mediate Th17 response
Yang et al. [20]	Elucidate alterations in HS-related gene expression in vivo and in vitro	In vivo functional genetic study (mouse model)	keratin 5-Cre-driven epidermis-specific *Ncstn* conditional knockout mutant in mice	Microarray; RNA-seq; RNAi	Notch downregulation drives the early upregulation of IL-36 and overexpression of Sprr2 in KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Zouboulis et al. [21]	Elucidate disease-driving mechanisms and tissue targeting.	Ex vivo human tissue analysis (transcriptomics) Observational human tissue data	HS lesional and non-lesional skin ($n = 12$)	Microarray; qRT-PCR; IHC	Calgranulin-A/B and serpin-B4 are detected in the hair root sheath; koebnerisin and connexin-32 in stratum granulosum; transcobalamin-1 in stratum spinosum/ hair root sheath.
Gambichler et al. [22]	Evaluate NOD2 pathway involvement	Observational human tissue data Ex vivo KC assay	HS lesional and non-lesional skin ($n = 19$) Cultured KCs from lesional sites	RT-PCR	Elevated expression of NOD2, hBD2, RNase7, psoriasin and SKALP/elafin in HS lesional skin Early upregulation of NOD2, RIP2, CARL and SKALP/ elafin in HS KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Navrazhina et al. [23]	Investigate immunological activity of tunnels	Observational human tissue data Gene-expression study	22 HS biopsies ($n = 22$); HCs skin ($n = 9$)	IHC; qRT-PCR	Dermal tunnels recapitulate the psoriasiform epidermal hyperplasia morphology of the overlying epidermis Tunnels are an active source of inflammation promoting disease progression Increased levels of IL-36α, CD117, CSF3, DEFB4B, CXCL1, CXCL8, KRT6, KRT13 are detected in epithelialized tunnels vs samples without tunnels Significant elevations of CXCL8 IL-36α, IL-17A/C/F in dermal HS tunnels
Song et al. [24]	Study human HS disease	In vivo functional genetic study (pig model)	Pig model carrying a precise *NCSTN* mutation	Single homology-mediated end joining based strategy; RFLP; IHC; Western blot; TEWL	Suppression of Notch-Hes1 signalling that in turn activates AMPK and inhibits cholesterol synthesis
Dajnoki et al. [25]	Detect inflammatory skin molecules in different stage disease	Ex vivo human tissue data (transcriptomics) Observational human tissue data	HCs AGR skin ($n = 8$); HS lesional and perilesional skin ($n = 10$)	RNAseq; RT-PCR; IHC; immunofluorescence	Activation of epidermal KCs in both non-lesional and lesional HS Upregulation of AMPs, IL-23, IL-1β, TNF-α in the interfollicular KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Frings et al. [26]	Characterize mRNA profile expression of HS epidermis	Ex vivo human tissue data (transcriptomics) Observational human tissue data Ex vivo KC assay	Lesional and perilesional HS epidermis ($n = 5$)	RNA-seq; qRT-PCR; Immunoblotting; IHC; Cell culture	Up-regulation of AP-1, substantial activation of JNK pathway and induction of STAT1 signature in lesional epidermis
Jin et al. [27]	Define the single-cell transcriptome of HS lesional epidermis and delineate the reprogramming of basal stem/progenitor cells	Ex vivo human tissue analysis (spatial transcriptomics) Ex vivo KC assay	HS lesional skin ($n = 7$); HCs skin ($n = 5$); Primary basal KCs culture	sc-RNA seq; flow cytometry; immunofluorescence; qRT-PCR; CRISPR/Cas9; mRNA-seq; CUT and RUN sequencing	Two KCs populations, POSTN/ASS1 and S100A clusters, are identified. Several clinically relevant inflammatory enhancers (and their TFs) are identified in CD49f^{high} HS basal cells S100A enhancer disruption reduces the production of HS-associated inflammatory regulators
Kim et al. [28]	Characterize the single-cell transcriptome of epidermal and dermal tunnel KCs	Ex vivo tissue analysis (trnascriptomic data)	HS skin ($n = 8$) (12 300 cells)	sc-RNA sequencing	HS dermal tunnel KCs cluster express high levels of IL-17C, IL-1A, IL-6 and IL-1B Epidermis KCs over-express IL-36γ and IL-1RL1 vs dermal tunnel KCs

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Schell et al. [29]	Assess epidermal inflammatory signature across different Hurley stage disease severity	Observational human tissue data Ex vivo KC assay	HS lesional skin SI ($n=11$); HS lesional skin SII ($n=41$); HS lesional skin SIII ($n=34$); non lesional skin ($n=9$); HCs skin ($n=39$) Cultured KCs	RT-PCR; Immunoblotting; IHC	Hurley Stage correlates with epidermal inflammation Significant CXCL3, IL-8, CCL3, CCL2, CCL22, IL-1β, TNF-α, IL-6, IL-36γ, IL-23A production by HS cultured KCs In the presence of IFN-γ, cultured KCs over-express IL-1β, IL-12, IL-23 and IL-36γ
Schi et al. [30]	Examine changes in hair follicle components in *NCSTN*-mutated mice	In vivo functional genetic study (mouse model)	C57BL/6 mice with an *NCSTN* mutation	Western Blot; IHC	Reduction of hair cortex cytokeratin, trichohyalin and Notch intracellular domain Development in mice of HS-like lesions after 6 months of age
Somogy et al. [31]	Investigate HS skin barrier integrity	Observational human tissue data	HS lesional skin ($n=10$); Peri-lesional skin ($n=10$); HCs skin ($n=10$)	qRT-PCR; IHC; TEWL; Confocal microscopy	Increased KRT6, KLK7 and DSG1 levels in HS lesional skin; in contrast KRT1 and KLK5 are detected in decreased levels No alterations in TEWL or epidermal structure between tissues analysed

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings

Adawi et al. [32]	Investigate differentially expressed genes in tunnel epithelium	Ex vivo tissue analysis	HS tunnel ($n=11$);
			HS tunnel stroma ($n=7$);
			SCC
			epithelia ($n=3$);
			SCC stroma ($n=3$),
			cyst
			epithelia ($n=3$);
			cyst stroma ($n=3$);
			HCs
			epithelia ($n=3$)
				Spatial transcriptomics	Defective intrinsic pathway for apoptosis and programme cell death are the most upregulated pathways
					NOTCH1 and WNT ligand biogenesis and trafficking are the most downregulated pathways
					TGFβ receptor signalling in EMT transition is over-expressed in both HS tunnels and SCC
					TGFβ receptor signalling is downregulated

Williams et al. [33]	Define the KCs response to GNAs	In vitro KC assay Observational human tissue data	KCs culture; C57bl/6 mice; fresh HS skin biopsies	RNA-seq; qRT-PCR; targeted cytokines assay; HIPR-FISH; IHC	*F. nucleatum* over-induces IL-6, TNF, CXCL1-8, CCL20 and the IL-17 pathway in KCs and recruits murine neutrophils and macrophages TLR4 and JAK inhibition attenuate the inflammatory response in KCs stimulated by GNAs
Zhang et al. [34]	Investigate the role of TLR2 upregulation in *NCSTN* and *PSENEN* knockdowKCs	In vitro KC assay In vivo functional genetic study (mouse model) Observational human tissue data	HaCaT cells; HS lesional skin; *Ncstn*$^{\Delta KC}$ mice	WES; RNA-seq; WB; IHC; immunofluorescence; ELISA; qRT-PCR	TLR2 agonist stimulation exacerbates levels of p-ERK1/2 and p-p38 MAPK

(Continues)

TABLE 1 | (Continued)

Author, year, reference	Rationale of the study	Type of evidence	Tissue analysed	Methods of assessment	Main findings
Du-Harpur et al. [35] (preprint article)	Characterize the cellular and molecular landscape of HS	Ex vivo human tissue data (spatial transcriptomics)	HS lesional skin	sc-RNA sequencing; spatial transcriptomics; IHC; microscopy	Critical interaction between migratory S100+ pathogenic keratinocyte state and COL6A5+ fibroblasts Interaction between (TLO)-like structures and APOD+ fibroblasts
Shishido-Takahashi et al. [36]	Examine the transcriptome of HGF-treated KCs	Observational human tissue data Ex vivo human tissue data (transcriptomics)	HS skin biopsies ($n = 9$); HCs skin ($n = 7$); Primary human adult epidermal KCs	RNA-sequencing; RT-qPCR; ELISA; IHC; sc-RNA sequencing	HGF induces the expression of EMT-related genes in KCs HGF-induced genes are over-represented in HS with tunnels

Abbreviations: AGR, apocrine gland-rich; AMPK, AMP-activated protein kinase; AP1, activator protein 1; CARL, cyclic amine resistance locus; CCK-8, cell counting kit-8; CCL, C–C chemokine ligand; CEA, carcinoembryonic antigen; CSF3, colony stimulating factor 3; CXCL, CXC motif chemokine ligand; DEFB, defensin beta; DSG1, desmoglein-1; EGFR, phosphorylated by epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; GNA, gram-negative anaerobic; hBD2, human beta-defensin-2; HGF, hepatocyte growth factor; HIPR-FISH, high-phylogenetic-resolution microbiome mapping by fluorescence in situ hybridization; HS, hidradenitis suppurativa; IFN, interferon; IHC, immunohistochemistry; IL, interleukin; interferon γ-induced protein 10 kD; JAK, janus kinase; JNK, c-Jun N-terminal kinase; KCs, keratinocytes; KRT, keratin; LCN2, Lipocalin-2; NCSTN; nicastrin; NcstnΔKC, Ncstn keratinocyte-specific knockout; NOD2, nucleotide binding oligomerization domain containing 2; ORS, outer root sheat; Pi3/AKT, phosphatidylinositol 3′ -kinase; qRT-PCR, quantitative real-time polymerase chain reaction; RAB31, Ras-Related Protein Rab-31; RIP2, receptor interacting serine/threonine kinase 2; RLFP, polymerase chain reaction—restriction fragment length polymorphism; RNAi, RNA interference; RNAse 7, Ribonuclease A Family Member 7; RNAseq, RNA sequencing; RT-PCR; real-time polymerase chain reaction; SCC, squamous cell carcinoma; SCD1, stearoyl-CoA 9-desaturase; scRNA sequencing, single cell RNA sequencing; SKALP, skin-derived antileukoproteinase; STAT, signal transducer and activator of transcription; TEWL, transepidermal water loss; TGF, transforming growth factor; Th, T helper; TLO, tertiary lymphoid organ; TLR, toll-like receptor; TNF, tumour necrosis factor; WB, western blot.

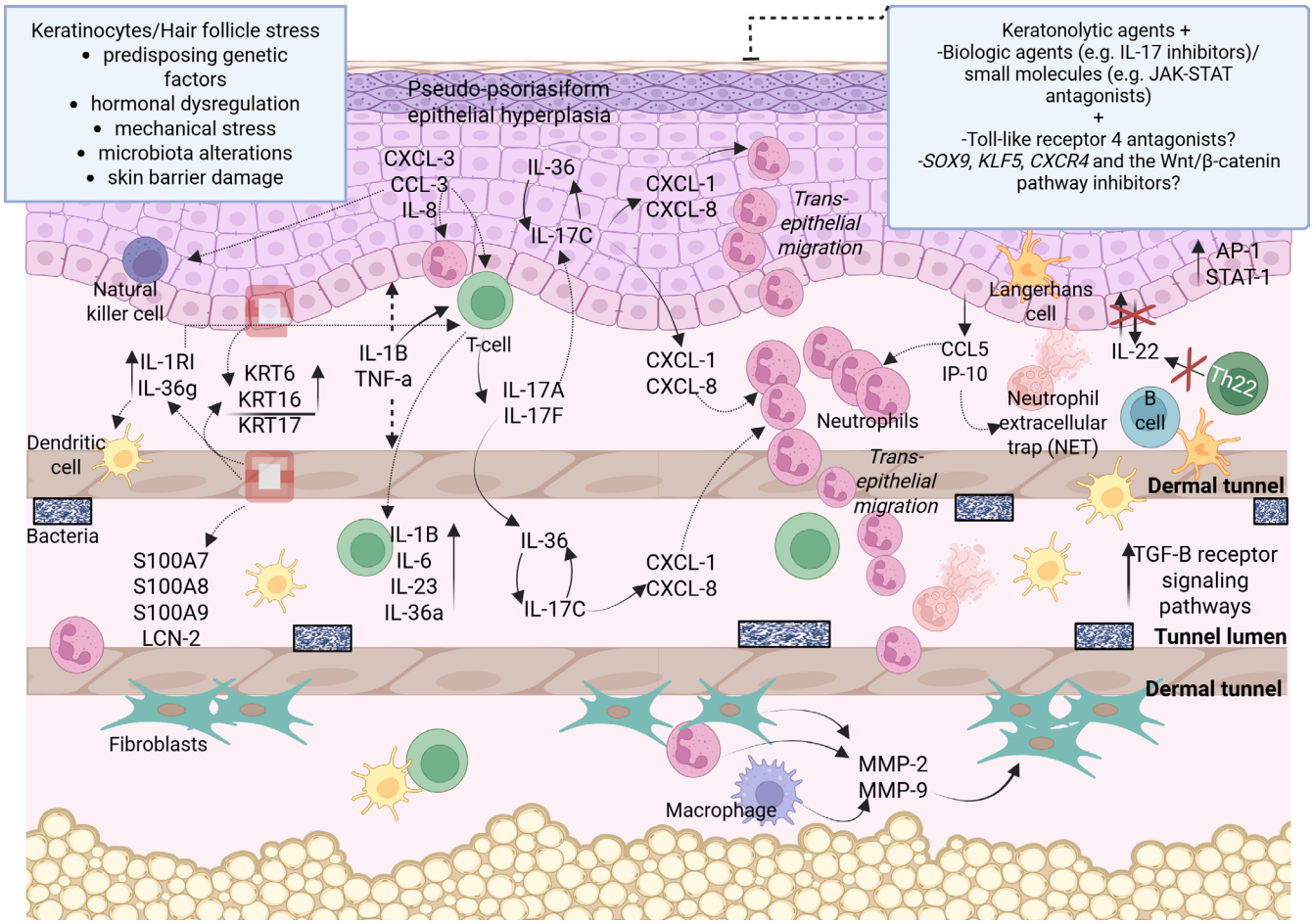

FIGURE 1 | The proposed role of KCs in HS pathogenesis. KCs could act as drivers of inflammation by integrating predisposing genetic factors, mechanical stress, hormonal dysregulation, microbiota alteration and immune-related signals. During early stages of disease (upper half of the figure) intrinsic KCs dysfunction triggers the release of CCL-3, CXCL-3 and IL-8, which in turn promote the recruitment of distinct immune cells, including neutrophils, CD8+ T cells and natural killer cells, to the epidermis. Then, immune-activated epidermal KCs express a wide array of proinflammatory cytokines and chemokines—such as TNF-α, IL-1β, IL-17C, IL-36, CXCL1 and CXCL8, which further drive the recruitment and activation of several immune cell types, including neutrophils, macrophages and dendritic cells. Crosstalk with Th1 and Th17 cells further amplifies inflammation through IL-17A/F-dependent signalling, also promoting the shift towards a dermal inflammation in later stages of HS (lower half of the figure). Dermal tunnels, typical of late HS, are characterized by highly proliferative keratinocytes forming a central lumen. Dermal tunnel KCs express several proinflammatory mediators including, among others, IL-17C, IL-1β, IL-6, IL-36α, CXCL1 and CXCL8, that could promote transepithelial chemokine gradients favouring immune cell recruitment and further inflammation. Tunnel KCs are also characterized by increased expression of K6, K16, and K17, S100A7/8/9 and neutrophil gelatinase-associated LCN2. Microbial dysbiosis and subsequent biofilm formation within the tunnel perpetuate the inflammatory context. Dynamic crosstalk among tunnel KCs, fibroblasts and immune cells—together with epithelial–mesenchymal transition (EMT)—the latter through overrepresentation of TGF-β receptor signalling pathway, drives tunnel persistence, thus sustaining HS late-stage chronic inflammation. Based on this pathogenetic model, targeting KCs activity and differentiation with keratinolytics, and immune-related inflammation with anti-IL-17 agents has already demonstrated efficacy in treating HS. Recent genetic studies have identified, among others, SOX9, KLF5 and CXCR4 as potential significant factors in the pathogenesis of HS, offering promising novel targets for therapeutic intervention. A thorough understanding of these genes could lead to increasingly effective treatment strategies.

papillary fibroblasts are necessary for the formation of these structures [35].

Additional signalling pathways and effector molecules have been seen to be differentially expressed in HS skin samples and KCs cultures, including *NOD2* (Nucleotide Binding Oligomerization Domain Containing 2), *RIP2* (receptor-interacting serine/threonine-protein kinase), *CARL* (cyclic amine resistance locus) and *SKALP/elafin* (skin-derived antileukoproteinase) [22]. During a specific experimental set-up to evaluate the response of unstimulated and Pam2/muramyl dipeptide (MDP)-stimulated primary (normal) KCs versus HS KCs isolated from lesional HS tissue, mRNA expression of *NOD2*, *CARL* and *SKALP/elafin* appears significantly increased in HS KCs compared with normal KCs at 6 h, while it decreased significantly at 48 h, suggesting an early upregulation of these genes in HS KCs. These results have also been confirmed when comparing HS lesional and perilesional skin, proving a pathogenic role of the NOD2 pathway and relative factors in the HS early active stage [22]. Therefore, HS KCs differ from normal KCs in terms of behaviour and timing, regardless of stimulation. It is worth mentioning that *NOD2* is also implicated in syndromic forms of HS [38] and some of its

well-known comorbid conditions such as inflammatory bowel disease [39].

Similarly, a state of severe epidermal stress characterized by a significant over-representation of AP-1-driven signature and STAT1 activation defines the keratinocytic gene expression pattern in HS [26]. This activation of STAT1 in the HS-affected epidermis may result from IFN-γ production and could promote the expression of key inflammatory genes, thereby orchestrating the activation of the innate immune system and the adaptive T-cell response in HS [26].

Taken together, all these findings confirm that epidermal and follicular inflammation is a hallmark of early HS, both in lesional and non-lesional skin. Basing on ex vivo and transcriptome approaches, an intrinsic pro-inflammatory signature in HS KCs, able to amplify innate immune response, has been proposed. In this theoretical framework, dysfunctional KCs act as primers of innate inflammation with the subsequent recruitment of different immune cells, which, in turn, promote a shift towards an adaptive Th1/Th17 immune response.

3.2 | Tunnel Keratinocyte Programmes

The characteristic feature of 'late' HS is the presence of dermal tunnels—also known as fistulae or sinus tracts. These structures, composed of a stratified squamous epithelium and tunnel-associated infiltrative-proliferative gelatinous mass in the lumen, have long been considered a fibrotic end-stage of the disease with unknown inflammatory contribution to HS [40]. Navrazhina et al. [23] overturned this vision, demonstrating that epithelialized tunnels drive a robust inflammatory response, expressing high levels of pro-inflammatory cytokines therapeutically targetable, at least in part dependent on IL-17 signalling. More specifically, tunnels are associated with increased gene expression of keratinocyte-derived factors, such as S100A7/8/9, psoriasiform pro-inflammatory cytokines and chemokines promoting neutrophil chemotaxis. In addition, a high amount of T cells, dendritic cells, neutrophil extracellular traps (NETs) and neutrophils is also present, as also supported by increased expression of neutrophil activation and transmigration marker, CD177 and CSF3 (colony stimulating factor 3), a cytokine belonging to the IL-6 family and involved in granulocytes production, differentiation and function. Lipocalin-2 (LCN2), a glycoprotein previously associated as a marker of IL-17-activated KCs [15], is also induced in the luminal layers of the tunnel epithelium [23], identifying it as a biomarker of disease activity [41]. Compared to epidermal KCs, dermal tunnels display increased mRNA expression of IL-17A, IL-17C and IL-17F [23], as also supported by a single-cell transcriptomics analysis conducted by Kim et al. [28]. Specifically, dermal tunnel KCs cluster over-express IL-17C and IL-1A in stratum corneum, while increased levels of IL-6 and *IL*-1B are detected in stratum spinosum and stratum basale, respectively [28]. HS tunnels also demonstrate higher expression of IL-36α, which is known to stimulate chemotaxis and immune cell activation. These findings suggest that secretion of IL-17C and IL-36α from epithelialized tunnels [23] likely leads to an increased expression of CXCL1 and CXCL8, which create a transepithelial gradient within the tunnel epithelium, which in turn amplifies neutrophil chemotaxis [23]. Additionally, a spatial transcriptomic preprint study by Marohn and colleagues showed that dermal tunnel KCs in HS express several genes including *WNT4* and *NRG1* (neuregulin 1), that interact with *FZD6* (frizzled-6) and *LSR* (lipolysis Stimulated Lipoprotein Receptor) expressed by plasma cells, potentially contributing to their specific recruitment [19].

Interestingly, KCs in HS dermal tunnels exhibited high levels of sebaceous and sweat gland-specific marker genes (*SCD1*, *CEA* and *SOX10*), suggesting that HS tunnels' origin cells might be multipotent epidermal stem cells with several glandular characteristics [19]. Despite this, KCs lining in HS tunnels showed a morphology and differentiation pattern matched with that of interfollicular epidermis, supporting the view that infundibulum's epidermal stem cells have dual cell fate [19].

When isolating the epithelium of HS through spatial transcriptomics, more than 700 differentially expressed genes (DEGs) and 200 dysregulated pathways have been retrieved [32]. KCs lining the tunnel lumen have a phenotype characterized by *KRT6A/16* overexpression and *KRT17*, which are also markers of highly activated and migrating KCs [32]. A marked gene expression of barrier alarmins *KRT6* and *KRT16* in HS lesional skin has also been reported by other research groups, with KRT6 elevation also confirmed by immunohistochemistry [31, 42]. Considering that KRT6 is a marker of activated and proliferative KCs rather than a barrier-forming molecule [36], this suggests that the patho-mechanism underlying HS initiation lies in abnormal KCs proliferation/inflammation rather than in a barrier defect [31]. The migratory behaviour of tunnels KCs may also be a consequence of epithelial-to-mesenchymal (EMT) transition-related pathways [11, 32]. Indeed, HS tunnels show an increased gene expression related to pathways for transforming growth factor (TGF)-β receptor signalling in EMT transition and a downregulated gene expression of TGF-β signalling, suggesting a shift of TGF receptor signalling in favour of EMT [32].

EMT-related pathways are also observed through RNA sequencing approach to be differentially expressed in hepatocyte growth factor (HGF)-stimulated KCs [11]. Basing on these transcriptomics findings, the authors infer that HS fibroblasts overexpress HGF, which binds c-Met on KCs and triggers an EMT programme in tunnel linings. HGF-driven upregulation of EMT-related transcription factors such as TWIST2 and the mesenchymal marker vimentin confers a migratory and invasive phenotype on keratinocytes, promoting the formation of epithelialized dermal tunnels [11].

Other important signalling pathways included those involved in the defective intrinsic pathway for apoptosis, suggesting that KCs have an apoptosis-evading property by causing the tunnels to acquire an invasive quality [32, 43].

Basing on these data, we can state that epithelialized dermal tunnels represent an active source of inflammatory mediators in the later-stage HS, although the exact role of tunnels KCs in this process remains to be fully defined. Transcriptomic data suggest that tunnel KCs are key players in tunnel formation, structure and expansion due to their migratory and invasive signature, but also as active producers of pro-inflammatory mediators such

as alarmins and chemokines which could trigger and sustain the tunnels' inflammatory microenvironment.

Overall, we can hypothesize that dynamic crosstalk among dermal tunnel KCs, fibroblasts and other immune cells—together with EMT—collectively drives tunnel expansion and persistence, thereby sustaining chronic inflammation in HS.

3.3 | Genetic/Epigenetic Regulation

The most reported genetic change associated with familial HS involves the *NCSTN* gene, whose encoded protein is a fundamental part of the gamma-secretase complex (GCS), a membrane-embedded complex that cleaves type I transmembrane proteins such as Notch [44, 45]. The latter is an evolutionary conserved cell signalling that is crucial for cell–cell communication and skin homeostasis through growth arrest and cell terminal differentiation [46]. Furthermore, Notch regulates the activity of both p21, which promotes cell cycle arrest in proliferating KCs [47], and p63, a master regulatory transcription factor required for both the proliferative and differentiation potential of developmentally mature KCs [20, 48].

An experimental study demonstrated that deleting the *NCSTN* gene through a keratin 5-Cre-driven epidermis-specific Ncstn conditional knockout mutant in mice recapitulates the major phenotypes of HS, including hair follicles hyperkeratosis, inflammation and severe cutaneous manifestations, highlighting that *NCSTN* deficiency and Notch-related downregulation appear to affect KCs proliferation and differentiation [30]. Interestingly, *NCSTN* deletion also results in marked early upregulation of IL-36a and Sprr2 (small proline-rich protein 2), which is associated with abnormal skin differentiation and barrier function. These findings suggest that *NCSTN* deficiency leads to impaired Notch signalling, which consequently drives the upregulation of inflammatory markers like IL-36 and Sprr2 in KCs [30].

Similarly, Shi et al. [24] found that *NCSTN* mutation in mice disrupts hair follicle development, causing abnormal structures that act as a model for human HS. The authors generated C57BL/6 mice with a *NCSTN* mutation and examined the expression of hair cortex cytokeratin and trichohyalin by Western blot and immunohistochemistry, in addition to Nicastrin and Notch intracellular domain (NICD). These mice developed HS-like skin lesions after 6 months, accompanied by downregulation of the aforementioned factors, indicating that *NCSTN* mutations disrupt the development of hair follicles through an impaired Notch signalling pathway.

Interestingly, a pig model carrying a heterozygous point mutation of *NCSTN* also simulated HS phenotype. This study demonstrated that the *NCSTN* mutation impairs secretase activity, reducing Notch signalling, which in turn disrupts cholesterol biosynthesis via the pAMPK-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) pathway, ultimately promoting skin barrier dysfunction and inflammation [12].

Defective *NCSTN* may affect KCs proliferation and differentiation not only through Notch, but also through other signalling pathways, including PI3K(phosphoinositide 3-kinase)/AKT [18], MAPK (mitogen-activated protein kinases) [17], EGFR (epidermal growth factor receptor) [49] and type I interferon pathways, disrupting the regular hair follicle cycle and contributing to the onset of clinical manifestations typical of HS.

To study alterations of biological signalling pathways modulated by *NCSTN* knockdown in KCs, Xiao et al. [18] used a human immortalized KC cell line treated with small interfering (si)RNA-targeted *NCSTN*, demonstrating that the PI3K/AKT is the most significantly activated pathway associated with KCs proliferation and differentiation. Moreover, AKT and phosphorylated (p) AKT levels are inversely correlated with NCSTN levels in KCs cultures, confirming that NCSTN loss may affect KCs functions mainly through NOTCH and PI3K/AKT signalling pathways. Subsequently, a defective NCSTN expression also leads to a decreased miR-100-5p expression, which in turn promotes p-AKT upregulation, thus resulting in KCs proliferation [17]. In addition, Ncstn KCs-specific-knockout mice showed that NCSTN loss leads to decreased levels of miR-30a-3p, which in turn negatively affected RAB31 expression [49]. The latter, through its over-expression, contributes to accelerate the degradation of activated EGFR, that is one of the most important pathways involved in growth, survival, proliferation and cell differentiation. In this way, the authors demonstrated that NCSTN/miR-30a-3p/RAB31 impairs EGFR pathway activation, thus favouring a dysregulated KCs differentiation in familial HS [49].

Besides *NCSTN*, the second most reported change in familial HS is in the Presenilin Enhancer 2 gene *PSENEN*, that acts as a regulatory component of GSC [34]. Zang et al. [50], through human immortalized keratinocyte line (HaCaTs) treated with potent short-hairpin RNA targeting *NCSTN* or *PSENEN*, reported that defective GCS components create a state where keratinocyte-driven inflammation is heightened through the TLR2 (toll-like receptor 2)/MAPK axis. This process contributes to the abscess formation, follicular destruction and chronic inflammation characteristic of HS, thereby identifying the TLR2/MAPK signalling pathway as a potential promising therapeutic strategy.

In addition to the 'classical' genes implicated in familial HS, recent genome-wide association studies (GWAS) are identifying other genes involved in follicular differentiation, keratinization and epithelial remodelling associated with HS risk and onset.

SOX9 (SRY-Box Transcription Factor 9) gene is emerging as a master regulator of hair follicle stem cells, specifically within the outer root sheath (ORS) and the bulge region. Mouse models lacking SOX9 manifest follicular degeneration, epidermal thickening and dermal scarring [51, 52]; furthermore, SOX9 has the potential to trigger an epigenetic reprogramming, which may contribute to the formation of sinus tracts with both interfollicular epidermis and glandular signature [19]. A recent GWAS conducted by Sun et al. [53] identified variants near *SOX9* and *KLF5* (Krüppel-like factor), the latter also involved in regulating epidermal stem cell (ESC) function. Variants at these loci are located in enhancer regulatory elements in skin tissue, particularly affecting keratinocytes and follicle regulation, which has led the authors to hypothesize that these or other nearby genes may be associated with the genetic risk of HS. Interestingly, *KLF5* deletion may lead to skin

barrier alteration, and its expression is lower in human disorders characterized by disrupted secretion of epidermal sphingolipids [54]. On the other hand, when overexpressed, KLF5 may promote hyperproliferation, hyperkeratosis and follicular occlusion as seen in murine models [55, 56]. It is noteworthy that SOX9 and KLF5 co-expression is transiently induced during wound healing, when stem cell populations are activated for repair, and the induced expression of KLF5 reduces the expression of SOX9. This homeostasis disruption could explain the formation of cysts and epithelialized tunnels lacking the typical differentiation into hair follicles or epidermis [53].

A genome-wide association meta-analysis of 4814 HS cases recently unravelled the involvement of Notch (*NCSTN*, *PSENEN* and *TMED10*—transmembrane emp24 domain-containing protein 10) and Wnt/β-catenin (*WNT10A*) signalling pathways, both related to epidermal keratinization and hair follicle/KCs proliferation and differentiation [57], thus confirming that an aberrant hair follicle formation contributes to the predisposing genetic background of HS [57–59]. Noteworthy, *SOX9* acts as a Wnt/β-catenin pathway antagonist [60] and its blockage should increase Wnt/β-catenin signalling pathway and keratinization [57], while *KLF5* overexpression may disrupt it [61]. These findings are especially important as further single-cell RNA sequencing and spatial transcriptomics analyses conducted by Perez et al. [62] showed that a specific subset of KCs localized in both surface and HS tunnel epithelium express *WNT10A*, one of the target genes retrieved from the above-mentioned GWAS [57], thus confirming its crucial role in hair follicle inflammation [60], although additional experimental validation is needed.

Khan et al. [63] in a recent preprint article experimentally validated a coherent gene module defined by upregulated *SOX9*, *CXCR4* (C-X-C chemokine receptor type 4) and *CD74* co-expression that maps to aberrant skin epithelial structures. Based on this model, CD74 in KCs cell membranes influences epithelial cell state by modulating inflammatory and cell proliferation pathways such as PI3K/Akt, WNT and apoptosis. Furthermore, NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signalling, via CD74 and CD44, contributes to the activity regulation of *SOX9*, *CD74* and *TNFAIP3* (TNF Alpha Induced Protein 3). All these genes appear upregulated both during early follicle development and throughout the hair follicle cycling, likely induced by CXCR4 inhibition in HS KCs. These results suggest that the blockage of CXCR4 may restore KCs homeostasis, acting as a novel therapeutic strategy for HS management.

Noteworthy, the same authors proposed a novel model that intersects with that of the main causing mutations of familial HS. Indeed, GCS loss-of-function mutations negatively affect CD74 processing, thus exacerbating PI3K/AKT-driven inflammation.

Based on these findings, it is widely accepted that genetic variants in the gamma-secretase complex found in familial HS disrupt follicular KCs differentiation, triggering a local inflammatory response, a mechanism confirmed through functional validation in animal models and in vitro KC studies. Beyond GCS-related pathways, genetic association study integrated with transcriptomic data suggests that HS is also driven by altered follicular and epidermal differentiation, keratinization and epithelial remodelling.

Overall, these findings increasingly converge on the concept that HS is fundamentally a disease of the hair follicle unit, thereby highlighting the alteration of the hair follicle as a core pathogenic mechanism and the pilosebaceous unit as the initial disease target [52].

3.4 | Upstream Triggers Converging on KCs State

3.4.1 | Mechanical Stress

An important aspect that deserves further investigation is whether skin barrier damage or other upstream trigger factors such as mechanical stress, hormonal changes and microbiome-derived signals may actively affect genetically sensitive KCs and trigger immune-mediated inflammation, thus resulting in the clinical development of HS.

It is well recognized that HS arises in intertriginous regions that experience recurrent friction and pressure. Chronic mechanical stress may increase the frequency of skin micro-injury, triggering the release of molecular patterns associated with cellular damage—resulting in the consequent release of pro-inflammatory cytokines—and allowing microbial penetration into the skin [64]. Additionally, in hair follicle biopsies from HS patients, a reduced number and volume of sebaceous glands have been observed [65]; these reductions are found even in unaffected skin, indicating that this defect is likely intrinsic to the hair follicle and precedes local and systemic inflammation. This reduction also results in the loss of antimicrobial lipids, potentially enhancing the risk of increased friction and micro-injury [66].

It has also been hypothesized that the effect of mechanical stress on HS arises from the loss of mechanical support provided by the pilosebaceous unit [67], leading to the assumption that friction and pressure may induce abnormal behaviour in KCs, including the increased proliferation of epidermal KCs via calcium signalling and pro-inflammatory cytokines release, which exacerbate interfollicular hyperplasia and hyperkeratosis [68–70]. Dysregulation of KCs function in HS can be further traced to reduced expression of keratin maturation markers KRT2e, 10 and 19 as well as adhesion molecules such as desmoglein 1 and desmocollin 1 in the inflamed epithelium, thus impairing wound healing and favouring hypertrophic scar tissue formation and tissue remodelling [71]. Major contributors to tissue degradation and remodelling are elevated levels of matrix metalloproteinase (MMPs) such as MMP2 and 9. Interestingly, an increased release of the latter in human KCs monolayer has been related to mechanical stress able to modulate KCs migration, representing an important aspect to explore, especially in specific HS phenotypes [72]. Of note, some wound healing-related genes such as *GJA1* (connexin 43), *LAMA5* (laminin subunit alpha 5), *IL-1A*, *EDN1* (endothelin 1) and keratinocyte growth factor undergo a downregulation in embryonic stem cell-derived keratinocytes in response to mechanical stress [73].

3.4.2 | Hormones

In recent years, increasing attention has been paid to the potential role of hormonal imbalance in the aetiology of HS, particularly that of sex hormones [74, 75].

Although the exact hormonal role in the pathogenesis of HS is not yet fully understood, a worsening of HS is often described by female patients during the premenstrual period and after pregnancy, suggesting that the effect of sex hormones on the cutaneous immune system may contribute to the onset, progression and severity of HS [76].

In addition to observational clinical studies, some functional assays were also conducted to assess the potential role of sex hormones and their immune-keratinocyte crosstalk. Higher proportions of androgen receptor (AR)–positive KCs are found in HS lesional skin, specifically in epidermis, infundibulum and tunnels of HS lesions when compared to unaffected skin [77], suggesting a possible role of AR in follicular occlusion and KCs proliferation. These findings are supported by some microarray studies, which revealed an enrichment of genes regulated by AR activation in HS regions compared to uninvolved skin areas. Of note, transcription factors associated with epidermal stem cell activity were also identified [78]. In another microarray-based transcriptomics study, a gender-specific gene expression profile in apocrine glands from HS lesional skin was observed; in women, an upregulation of gene signatures involved in androgen-regulated testicular differentiation was detected, while in male patients with HS, a downregulation of genes related to lipid metabolism was found [79].

In summary, although further studies are needed, hormonal dysfunction, particularly excessive androgen signalling, appears to trigger a chain reaction where keratinocytes fail to differentiate properly, proliferate uncontrollably and produce inflammatory signals, resulting in the characteristic lesions of HS [80].

3.4.3 | Microbiome-Derived Signals

The chronic inflammation observed in HS may also be driven by microbiome perturbations [81]. As demonstrated by Ring et al. [82], in HS chronic lesions, biofilms aggregated in approximately 75% of sinus tracts and infundibula sharing several similarities with biofilm infections. The deposition of scattered intradermal corneocytes and hair fragments as well as abundant keratinous debris in HS lesions may promote biofilm formation by commensal bacteria, thus potentially enhancing their pathogenic properties and related inflammation in chronic HS lesions [82].

The skin microbiome in HS exhibits significant dysbiosis, characterized by a reduction in commensal bacteria such as *Cutibacterium acnes* and an increased abundance of anaerobic and opportunistic bacteria. This shift, mainly in the hair follicles and lesions, suggests that a dysbiotic microbiome contributes to the chronic inflammation and pathogenesis of HS [33, 83]. An experimental study conducted by Williams et al. [16] indicated a specific HS microbiome characterized by an abundance of gram-negative anaerobic (GNA) bacteria such as *Fusobacterium Nucleatum* (FN) and *Prevotella* species, although there is still no direct evidence of the cutaneous KCs barrier response to GNAs. The authors demonstrated that normal KCs stimulated in vitro with IFN elicit a specific inflammatory signature; this profile is different from that caused by gram positives, thus suggesting a specific and unique activation pattern for GNAs. Notably, this pro-inflammatory signature GNAs-induced overlaps with transcriptome profile of HS patients' biopsies and murine models and, more interestingly, bacteria are spatially associated with activated KCs in HS tunnels. Finally, the same authors demonstrated that both TLR-4 and pan-JAK inhibitors attenuate pro-inflammatory cytokine production from KCs stimulated by GNAs, underlining their therapeutic potential [16].

Another interesting aspect concerns antimicrobial peptides (AMPs), key components of innate immunity which may have pro-inflammatory or anti-inflammatory effects [84]. Keratinocytes isolated from hair follicle of HS patients produce a distinct and altered pattern of AMPs in response to microbial products, when compared to normal KCs [13]. This alteration of AMPs may also be due to an altered IL-22 signalling in HS, a cytokine critical for AMP induction; Jones et al. [85] observed lower levels of IL-22 in the cultured KCs supernatant from HS patients compared to controls while Wolk and colleagues [86] showed a relative deficiency of IL-22 levels in HS skin compared to other chronic inflammatory diseases [13, 85–86]. IL-22 is a member of the IL-10 family and is secreted by different types of immune cells including IL-22(+) CD4(+) T cells (Th22), Th17 and IL-22 expressing innate leukocytes (ILC22) [87]. Accumulating evidence reports that IL-22 secreting CD4+ T cells are not enriched in HS lesional skin [13], further suggesting that an altered production of IL-22 by immune cells could affect KCs response, thus contributing to an altered AMPs production.

An upregulation of AMPs secretion is also induced by an increased prevalence of *Prevotella* and *Porphyromonas* spp. in HS skin that leads to an increase in KCs proliferation and recruitment of other immune cells, thus culminating in follicular occlusion [84].

4 | Major Open Questions

To date, our knowledge of HS pathophysiology within the context of its clinical heterogeneity is still fragmented. While HS is believed to be a multifactorial disease caused by a close interaction between lifestyle risk factors, genetic predisposition, immune dysregulation and alterations in the skin microbiome, the precise mechanisms underlying these interactions remain elusive. Ongoing questions mainly regard the precise mechanisms orchestrating immune cell recruitment, their interactions at different disease stages, and their interplay with non-immune cells in determining local inflammation. The contribution of keratinocytes requires further investigation as well. Indeed, given the emerging multifaceted role of keratinocytes in the overall pathophysiology of HS, it will be critical to determine at which stage of the disease they compete most. It will be equally important to determine the pathogenic nature of interactions with other immune cells, mainly neutrophils, and key inflammatory signalling pathways to guide novel potential targeted and combination therapies.

5 | Conclusions and Perspectives

HS is a heterogeneous cutaneous disorder, whose drivers of onset, activity and progression as well as modulators of treatment response are influenced by a wide range of factors. The

inflammatory environment represents one of the most important targets which require targeted consideration for holistic therapeutic strategies. Distinct immune cells and also keratinocytes are emerging as crucial players in the inflammatory response and overall pathophysiology of HS. Although further targeted research is needed, advances in knowledge have led to consider keratinocytes not only targets of inflammatory signalling pathways in HS but also active producers of pro-inflammatory cytokines, chemokines and effector molecules that may influence disease onset and activity. Indeed, gene expression studies and transcriptomic data highlight KCs' pro-inflammatory signature in both early and late HS alongside the possible contribution in tunnels formation and expansion in later-stage HS.

Even in familial forms of HS, an important role of keratinocytes has been demonstrated. In fact, the presence of gamma-secretase genes mutations impairs KCs functions, leading to dysregulated KCs differentiation and abnormal proliferation, thus contributing to HS phenotype.

In conclusion, given the emerging role of keratinocytes, further studies are needed to better characterize their inflammatory signature and genetic profile as well as the interplay with other immune cells. In this regard, it has been demonstrated, in other inflammatory disorders such as atopic dermatitis, that KCs critically control the threshold of inflammatory signalling in the skin by inhibiting T cell proliferation and cytokine production [88]. Determining whether the defect in keratinocyte formation triggers the immune system, or whether it is instead the activation of the immune system that triggers this inflammatory response in keratinocytes, is another particularly interesting topic to better explore in the context of HS. Another aspect worthy of further investigation is whether damage to the skin barrier or other trigger factors—such as mutations, mechanical stress, hormonal changes and microbiome imbalance—may activate genetically susceptible keratinocytes and trigger an immune-mediated inflammation, thereby leading to the clinical development of HS. Finally, the identification of specific keratinocytes clusters with unique signatures could potentially allow the identification of future therapeutic targets. Indeed, translational evidence obtained to date demonstrates that epidermal hyperkeratinisation is central in HS pathophysiology, potentially reinforcing the role of keratolytic agents in the treatment landscape of HS [89].

Azelaic acid (AzA) is commonly used in acne, but literature data support its use as an adjunctive treatment for HS, particularly in paediatric patients and when combined with topical clindamycin [90, 91]. A 20% AzA cream has demonstrated a keratolytic effect on both normal and acne-affected skin, associated with a reduction in follicular hyperkeratosis. It also has bacteriostatic and bactericidal properties, but does not affect sebum production and composition, or sebaceous glands morphology [92].

Retinoids are a class of chemical compounds consisting of vitamin A and related derivatives. The therapeutic arsenal for HS includes both topical and systemic retinoids, due to their keratolytic action and anti-inflammatory properties [93]. As for topical retinoids, there is still no formal assessment of their efficacy, although third-generation topical retinoids such as adapalene and tazarotene have demonstrated an important anti-inflammatory activity [90]. Systemic retinoids, particularly isotretinoin and acitretin, are also considered as a potential HS treatment. Although some retrospective studies report a significant lesion improvement with isotretinoin [94, 95], its use is often disappointing and the reported data are inconsistent [89, 96]. Acitretin reduces the rate of keratinocyte proliferation as well as epidermal/dermal inflammation by inhibiting leukocyte chemotaxis and proinflammatory mediator's release. It may be more effective than isotretinoin and can be considered in early HS stages or in the presence of hyperkeratotic follicular lesions [89, 97–98].

It is important to emphasize the systemic retinoids are highly teratogenic and must not be used during pregnancy. They require strict adherence to a Pregnancy Prevention Programme (PPP), including mandatory contraception for at least 1 month before, during, and 1 month after treatment [99].

Resorcinol is another keratolytic and anti-inflammatory topical agent that showed a significant improvement of Hidradenitis Suppurativa Clinical Response (HiSCR) and pain in a retrospective study consisting of 134 HS patients [100]. A case series also reported its efficacy in mild HS in terms of inflammatory activity and pain reduction in all treated patients [101]. Overall, although the use of resorcinol is still poorly documented in the literature, it is typically used for the short-term management of HS flare-ups, which confirms its role as a valid alternative [102].

In conclusion, in this growing body of knowledge, 'old' and novel keratolytic agents should be considered, in combination with biologics such as IL-17 antagonists and/or small molecules like JAK/STAT inhibitors, as part of therapeutic strategies for HS [89, 103]. Also understanding the roles of *SOX9*, *KLF5*, *CXCR4* and the Wnt/β-catenin pathway in HS pathogenesis could lead to novel treatment strategies.

Author Contributions

Conceptualization C.M., M.R., and A.V.M. Data Curation C.M. and M.R. Formal Analysis C.M. and M.R. Funding Acquisition A.V.M. Investigation C.M. and M.R. Methodology C.M. and M.R. Project Administration C.M., M.R. and A.V.M. Resources C.M. and M.R. Supervision A.V.M. Validation C.M. and M.R. Writing – Original Draft Preparation C.M. and M.R. Writing – Review and Editing M.R. and A.V.M.

Acknowledgements

This work was partially supported by the Italian Ministry of Health (Ricerca Corrente) of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy).

Funding

This work was supported by the Italian Ministry of Health (Ricerca Corrente) of Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan (Italy).

Conflicts of Interest

Chiara Moltrasio and Maurizio Romagnuolo have no competing interests to declare. Angelo Valerio Marzano reports consultancy and/or advisory board honoraria from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Galderma, Incyte, Johnson and Johnson,

Leopharma, MSD, Novartis, Otsuka, Pfizer, Sanofi-Regeneron, Takeda and UCB.

Data Availability Statement

All data are present in the main text, in the table and in the graphical abstract.

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