Hidradenitis suppurativa: A folliculotropic disease of innate immune barrier dysfunction?

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Abstract
The innate immune system of human skin consists of a multi-layered barrier consisting of cells and soluble effector molecules charged with maintaining homeostasis and responding to insults and infections. It has become increasingly clear that these barrier layers become compromised in skin diseases, especially in disorders of an (auto)inflammatory nature. In the case of hidradenitis suppurativa, great strides have been made in recent years in characterizing the underlying breakdown in homeostatic innate immunity, including an increasing understanding of the central role of the hair follicle in this process. This breakdown appears to occur at multiple levels: the pilosebaceous unit, associated epithelium, the cutaneous microbiome, alteration of immune cell function and local molecular events such as complement activation. This review seeks to summarize, contextualize and analyse critically our current understanding of how these innate immune barriers become dysregulated in the early stage(s) of hidradenitis suppurativa, and to speculate on where potential hidradenitis suppurativa research could be most fruitful.

KEYWORDS
barrier, hair follicle, hidradenitis suppurativa, inflammation, innate immunity

1 | INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease affecting the axillae, perineum and inframammary regions, among other body sites. Accumulating evidence indicates a hair follicle (HF) focus to this disease, as it is characterized by an early occlusion, followed by rupture of the HF and more generalized skin inflammation.1 HS is part of the follicular occlusion tetrad of disorders (HS, acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus). It results in painful local nodules and abscesses that can develop into pus-filled malodorous sinus tracts, also known as tunnels, that may result in extensive scarring.2,3 In addition to cutaneous inflammation, patients with moderate-to-severe HS have evidence of systemic inflammation, as measured by C-reactive protein (CRP) and high-sensitivity CRP.4-8 Thus, it is unsurprising that HS is associated with significant psychosocial morbidity and profoundly impaired patient quality of life, when compared to other inflammatory skin diseases such as psoriasis.9-12 Aside from the obvious pain and discomfort of HS lesions, patients commonly experience mood disorders (eg depression), altered body image, stigmatization, social isolation and sexual dysfunction.9,12-16 Approximately 35% of HS cases in northwestern European cohorts display a positive family history which suggests a genetic component.17 This is less in some Asian populations at approximately 5% of patients.18,19 Environmental factors,
particularly obesity and smoking, increase the risk of developing the disease. Treatment options for HS are often unsatisfactory.

While immune dysregulation is a crucial aspect of HS pathophysiology, the HF is the initial or very early, focus/target of the disease. An early event in HS pathogenesis involves a disturbance of the distal HF epithelium that causes blockage of the upper HF, which triggers a cascade of events centred in and around the HF. These include aberrant, uncontained, follicular keratinization, which may be a significant further trigger for immune dysregulation and inflammation. Our skin’s multiple “barriers” (eg stratum corneum, HF and sweat gland ostia, and melanized epidermis stratum basale) provide a strategically located interface for our innate immune system to detect, sense, interpret and rapidly respond to the myriad danger signals (including microbial insults and “damage” products) in order to maintain and restore skin homeostasis.

In diseases such as HS, aberrant innate immune responses lead to severe inflammation with inappropriate responses that either triggers or fails to resolve further inflammation, leading to a failure of effective tissue remodelling and repair. This review seeks to analyse our current knowledge of the disordered innate immune responses and barrier disruption in HS, with a particular focus on the HF. We believe a better understanding of the involvement of the HF in HS may be crucial to HS pathogenesis and may help to inform future therapies.

2 | HS BARRIER DYSFUNCTION: THE SKIN AND PILOSEBACEOUS UNIT

2.1 | Hair follicles, the origin of HS?

The origins of HS are thought to involve perturbation in the homeostasis of the pilosebaceous unit, which includes the HF, sebaceous gland and arrector pili muscle. The mechanism(s) by which this perturbation occurs is unclear (Figure 1). Established by week 12 of human gestation, the development of this mammal-specific trait involves a series of complex cell fate decisions across multiple cell populations to produce a continually cycling mini-organ. Life-long cycling (the only human adult tissue to do so) involves production of hair fibres during anagen (Figure 1A), followed by an apoptosis-driven regression of approximately two thirds of the HF’s cellular mass during catagen, and a period of relative rest during telogen until the next anagen phase re-starts the cycle. In intertriginous regions of the skin, the pilosebaceous unit is further expanded to include apo-eccrine or apocrine glands. These glands were thought originally to be important in HS, but are now considered to be secondary in disease pathogenesis. A recent study by Dunstan et al has shown that HS may also emerge from the infundibulum of smaller vellus hair follicles, which would appear to downplay further a role for apo-ecrine or apocrine glands. However, there is evidence that apocrine glands, as well as cells from the outer root sheath (ORS) of the HF, secrete excessive levels of antimicrobial cathelicidin, which may trigger inflammatory responses. Several studies have reported that in early HS lesions, the upper HF (or infundibulum) becomes dilated and occluded, and may demonstrate parakeratosis (Figure 1B). Some of the latter changes can also be seen in perilesional HS tissue, suggesting that they are involved in very early disease, and may be a feature of skin with increased susceptibility to HS pathology. Follicular keratin plugging can generate a build-up of bacteria, sebum and HF cellular debris, which may contribute to further HF stress that culminates in rupture. The latter is associated with the further release of noxious stimuli, which can be sensed by macrophages and other inflammatory innate immune cells (Figure 1C). Among these stimuli are keratins derived from the hair shafts themselves, which have been reported to often appear in the keratin squamous epithelium-lined cysts or sinuses in the deep dermis of HS lesions. The presence of these large, digestion-resistant entities in the dermis may generate a foreign body response and explain the increased frequency of giant cells observed in these lesions. Immune cells then release cytokines and chemotaxins that activate the surrounding stroma and epithelia, including the epidermis, as well as recruiting further leukocytes, especially neutrophils.

The causes of initial HF disturbance, including occlusion, in HS remain unknown, but there have been some recent insights into this process. A hallmark of the HF is its regenerative capacity, whereby in extremis (eg loss of epidermis through injury) epithelial stem cells located in the so-called “bulge” of the HF can aid regeneration of the interfollicular epidermis. It is worth noting that the stratum basale of the epidermis is anatomically continuous with cells of the HF ORS (Figure 1A). Orvain et al. have recently suggested that loss of quiescence in the stem cell bulge of HFs from HS patients may be associated with excessive proliferation of ORS keratinocytes. While these authors suggested that this effect was not seen in the interfollicular keratinocytes from the same patients, we consider that some increased recruitment of epidermal progenitor keratinocytes is also likely to underpin the psoriasiform changes reported in the HS interfollicular epidermis. Loss of epithelial HF stem cell quiescence is reported to be mediated by innate immune sensing of cytosolic DNA, although it is not yet clear what stimuli lead to the DNA damage in these cells in the first place, and whether this damage is intrinsic or extrinsic to the HF (Figure 1B). This paradigm might explain the generation of epidermal tendrils (forerunners of tunnels) from the HF infundibulum as reported by Dunstan et al. These authors propose that the disruption of these HF keratinocytes in HS lesions is associated with other abnormalities in the expression of genes associated with innate immunity, including the elevated expression of antimicrobial S100 proteins in the ORS and inner root sheath (IRS) that are normally associated with activated neutrophils. The cause of this inflammatory gene signature is unknown, although contributions from IL-17A signalling and alterations to the HF microbiome are distinct possibilities. As such, how these expression patterns may contribute to the disruption of HF homeostasis is yet to be determined.

Several other aspects of HF involvement in HS remain unclear, not least whether a HF is more susceptible during a particular phase
of the hair growth cycle (eg the highly proliferative anagen phase), given that the cycle overall involves extensive periods of tissue remodelling, as well as the coordinated involvement of immune cells such as macrophages and T cells.\textsuperscript{26,39,40} Moreover, the transient components of the growing or anagen HF epithelium enjoy rare “immune privilege,” a feature that is purported to “collapse” in a variety of both reversible and scarring alopecias.\textsuperscript{26,41} Whether a similar scenario is relevant in HS is not yet clear given that the initial target of HS is rather the immunocompetent infundibulum, that is of the upper permanent part of the HF. The advent of spatial transcriptomic and proteomic technologies promises to help answer some of these open questions, particularly regarding the spatiotemporal dynamics of this complex cycling mini-organ in disease progression.

2.2 | Keratinocytes

Disruption to normal integument barrier function is a feature of HS, where it can be characterized in part by a keratinocyte hyperplasia in both epidermis and more localized in the inflammatory nodules of affected lesions.\textsuperscript{42} The keratinocyte-rich epidermis is the skin barrier that interfaces most with the environment, including via its resident cutaneous microbiome, and is organized within strata of increasing cellular differentiation/keratinization/cornification.\textsuperscript{43} Whole exome sequencing of patients with PAPASH, a syndrome including pyogenic arthritis, acne, pyoderma gangrenosum and HS, has revealed mutations in genes involved in keratinization and cornification.\textsuperscript{44} This has led to the characterization of HS as an autoinflammatory keratinization disease.\textsuperscript{45,46} In a study by Kurzen et al, altered epithelial differentiation profiles were demonstrated in HS, using an immunohistochemical approach, and three associated pathological phenotypes were proposed based on the expression of a wide range of cytokeratins (CK) and desmosome-associated proteins.\textsuperscript{47} HS tissue was marked by expression of CK6, 13, 15, and 16, with the most inflamed subtypes displaying elevated CK19 and loss of CK10 expression. In addition, the expression of the infundibulum-associated CK17 was lost in HS-affected HFs, which was confirmed in a subsequent study.\textsuperscript{48} This dysregulation of keratin expression has

FIGURE 1 | Disruption of the pilosebaceous unit and HS. The pilosebaceous unit consists of the hair follicle (HF), sebaceous gland and arrector pili muscle (A). In HS, loss of stem cell quiescence in HF stem cells (HFSC) in the critical bulge region, via DNA sensing through the IFI16/STING pathway, may lead to hyper-proliferation, hyper-keratinization and HF plugging (B). This may in turn lead to tendril formation and cyst development. Physical impairment of the HF and associated cysts causes a build-up of keratin, sebum products, bacteria, dead/dying cells and other inflammatory stimuli (C). Collectively, these are sensed by cells of the innate immune system (eg macrophages), which thereafter propagate the extraordinary and highly destructive inflammatory response seen in HS. Figure created using BioRender.com.
been suggested as a source of HS draining sinus epithelium fragility, predisposing it potentially to rupture and subcutaneous abscess formation.\textsuperscript{35,49,50} Dunstan et al. have described elevated CK5 and CK10 expression in early HS lesions, with a more random pattern of CK expression during disease progression.\textsuperscript{31} CK16 is elevated in perilesional and lesional HS tissue and is especially pronounced in epithelial tunnels, where its expression is no longer limited to basal keratinocytes.\textsuperscript{51,52} These studies collectively suggest an alteration in epithelial differentiation profiles towards a hyperproliferative and inflammatory state. However, this area of the field could be greatly advanced using more sophisticated transcriptomic and multiplex protein imaging technologies. The localization of keratinaceous material in HS tissues (using pan-keratin as well as HF-specific keratin antibodies) will also be important, as it supports the hypothesis that these proteins are potent immunogenic stimulators.\textsuperscript{29,34-36} A summary of the CKs altered in HS is presented in Table 1. Keratinocyte function is altered in several other ways in both lesional and perilesional HS skin, including via inflammatory cytokine signalling, wound healing and antimicrobial peptide (AMP) secretion.\textsuperscript{53-56} For instance, keratinocytes from HS lesions secrete excessive levels of the pro-inflammatory cytokines IL-1\textbeta, tumour necrosis factor (TNF)-\alpha and IL-23; the latter is speculated to start an autocrine and paracrine inflammatory loop.\textsuperscript{57} The targeted ORS keratinocyte population demonstrates increased inflammatory activity in the form of interferon (IFN) release. This is not a feature of the adjacent histologically similar keratinocytes of the stratum basale layer of the epidermis.\textsuperscript{37} This may reflect some specific influence of the infundibular keratinocyte environment that is not present in interfollicular epidermis.

Sinus tracts, or tunnels, are a striking feature of advanced HS, and keratinocytes have been shown to be immunologically active in their formation.\textsuperscript{51} Indeed, the “tendril hypothesis” has been advanced to suggest that the origins of HS lie in HF keratinocyte hyperplasia that leads to the increasingly immunogenic projection of epithelia into the dermis.\textsuperscript{33} These epithelial defects not only alter the integrity of the skin barrier, including the composition and crosstalk with the skin microbiome, but also gradually and increasingly disrupt skin homeostasis/differentiation including via disrupted CK expression.\textsuperscript{47,48,58-61} Similar alterations in keratinocyte barrier biology occur in other dermatoses, such as psoriasis (including projections of the epidermis-derived epithelium into the deep dermis). Thus, in striking contradistinction to these other hyperproliferative skin disorders, the early perturbation of the pilosebaceous unit strongly supports the involvement of hair growth-specific elements to early HS pathology.

3 | SENSING THE DANGER: INNATE IMMUNE CELLS IN HS

Although still lacking formal proof, it is likely that the primary induction of significant inflammation in HS derives from signals secreted from perturbed keratinocytes located in the upper HF, and so is an indirect or secondary consequence of activated cell types of the innate immune system. These activated immunocytes shape the subsequent adaptive inflammatory Th1/Th17 cell and B-cell expansion seen in HS, as well as contributing to tissue fibrosis and auto/neoadjacent generation. The explosive nature of the associated cytokine “Molotov”-cocktail, produced by myriad stimulated immune and non-immune cells, appears to be critical in this process, as will be discussed below.

3.1 | First responders in HS: antigen-presenting cells

Antigen-presenting cells (APCs) appear to be an early recruit in the HS inflammatory cascade, and at this stage include macrophages and dendritic cells (DCs) that mediate crosstalk between the innate and adaptive immune systems. These APCs are likely to be important in early HS inflammation, particularly due to their expression of toll-like receptors (TLRs), their capacity to phagocytose free-keratin (potentially HF-derived) in the dermis and their secretion of multiple

| Cytokeratin (CK) | Expression (HS lesion vs healthy skin) | Region | Associated processes/roles | References |
|-----------------|----------------------------------------|--------|---------------------------|------------|
| CK5             | ↑                                      | Epidermis, sinus epithelium | Stratum basale cytoskeleton | 47         |
| CK6             | ↑                                      | ORS, stratum spinosum | Inflammation and wound healing | 20         |
| CK10            | ↑                                      | Epidermis, cornifying tendrils | Infundibulum differentiation marker | 31,47      |
| CK13            | ↑\*                                    | Non-cornifying sinus tract | Suprabasal cytoskeleton | 47         |
| CK14            | ↑                                      | Stratum basale, sinus tracts | Stratum basale cytoskeleton | 47         |
| CK15            | ↑\*                                    | Infundibulum tendrils | HF stem cell marker | 31         |
| CK16            | ↑                                      | ORS, stratum basale/spinosum | Inflammation | 20,47,48,51 |
| CK17            | ↓                                      | Infundibulum | Keratinocyte survival and growth | 47,48      |
| CK17            | ↑\*                                    | Infundibulum tendrils | Keratinocyte survival and growth | 31         |
| CK19            | ↑\*                                    | Sub-sebaceous gland | Skin stem cell marker | 31,47      |

*=indicates increased expression, or expression in different locations compared to healthy skin.
The antigen repertoire presented by these APCs to the adaptive immune systems is wholly unknown at this stage, but is under active investigation.

Macrophages are the main producers of IL-1β and TNF-α in HS; two cytokines that appear critical in establishing an inflammatory response. In addition, APCs have been implicated in the generation of high levels of matrix metalloprotease 2 (MMP2) in HS lesions, which may blunt AMP function. Specifically, CD68⁺ and CD32⁺ macrophages co-localize with IL-12 and IL-23 expression in HS tissue, which dictate Th1 and Th17 polarization, respectively.

Byrd et al. have demonstrated that macrophages expressing the anti-inflammatory M2 marker CD163 can induce fibrosis in the later phases of HS pathogenesis by inducing fibroblasts to deposit collagen via CCL18 secretion. Moreover, macrophage migration inhibitory factor (MIF) levels are elevated in HS, which would also suggest the involvement of a more inflammatory macrophage phenotype.

This is supported by recent scRNA-seq findings showing that inflammatory M1 macrophages predominate and anti-inflammatory M2 macrophages are depleted in non-lesional HS skin.

By contrast, the potential role of DCs in HS is understudied, given their importance in shaping pathological T-cell responses. Several studies, using markers like CD1a, CD11c, CD207 and CD209, have reported an influx of DCs into HS-affected skin. Meanwhile, scRNA-seq approaches are also shedding light on DC subsets in HS, with numbers of activated conventional 1 DCs (cDC) appearing to be increased in HS lesions, whereas type-2 DCs are reduced. With functional MHCII and a capacity to induce T-cell responses, these cells are critical determinants of other inflammatory dermatoses (eg psoriasis and atopic dermatitis). It is not clear where DC originate from in HS and there is also scant information on the involvement of the uninvolved skin/upper HF resident Langerhans cell in HS. The latter have been shown to migrate into the usually immune-privileged lower HF during inflammatory changes associated with alopecia areata.

While monocytes contribute to HS-related leucocytosis, their contribution to the APC pool, for example through their differentiation towards DCs or macrophage subtypes, is unknown. These cells are critical for dictating the initiating events of inflammation and so may present attractive therapeutic targets, especially in early HS disease, warranting further research. Another APC, the B cell, regarded normally as an adaptive immune cell, has also been proposed as a potential driver of HS pathogenesis.

3.2 | HS inflammation propagators: neutrophils and other granulocytes

Neutrophil recruitment and activation appear to be an important next step in driving HS pathogenesis. These cells are also implicated in several autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, due to their extensive repertoire of pro-inflammatory mediators (including cytokines and tissue-remodelling/antimicrobial enzyme-loaded granules), as well as their phagocytic capacity. Neutrophils are present in elevated levels in HS peripheral blood and can be recruited easily in response to chemokines released during initial barrier perturbation. Neutrophil numbers in HS lesions correlate with disease severity, particularly pus formation and chronicity. The active release of cellular contents including enzymatic granules and extruded nuclear chromatin, termed neutrophil extracellular traps (NETs), is a critical part of the neutrophil’s defensive armoury, but can be deleterious to maintenance of tissue homeostasis. For instance, NETs are a source of citrullinated autoantigens in SLE and Byrd et al. have demonstrated that this paradigm also holds true in HS, with increased NETosis seen in an African-American HS cohort and resultant autoantibody formation that correlated with disease severity.

Moreover, released DNA can stimulate APCs to amplify inflammation through IFN release. The contribution of extracellular traps from other cell types in HS, such as eosinophils or macrophages, has yet to be explored. With regard to neutrophilic granule release, Lapins et al. reported no difference in elastase activity between peripheral neutrophils of HS and control individuals, but did note an increased capacity in HS neutrophils to generate reactive oxygen species (ROS) in response to stimulation. Lima et al. reported that myeloperoxidase (MPO) expressing neutrophils are the most abundant IL-17-expressing cells in HS lesions, although IL-17 expression was lower in these granulocytes than in CD4 T cells. S100A8/9, a feature of neutrophil-specific granules, is also elevated in both HS epidermis and serum and may play a role in innate immune activation. Its dual increased expression (ie locally and systemically) points to unresolved temporal aspects of the disease. That is, does initial local S100A8/9 expression induce subsequent neutrophil activation? Navrath and others have recently argued that HS is a systemic neutrophilic dermatosis, based on the expression of neutrophil markers lipocalin-2 (LCN2) and IL-17A. Still, the direction of causality in disease progression and HS comorbidities remains an important open question. In this context, dapsone therapy, which targets neutrophil-mediated inflammation, may lead to clinical improvement in HS patients.

While a role for other granulocyte populations in HS pathogenesis was initially dismissed, this picture has changed recently. For example, mast cells appear to be elevated in HS lesions and pruritus, often associated with histamine release, is a common but under-reported feature of this disease. Indeed, CD117⁺ mast cell numbers correlate with HS activity and severity. Eosinophil numbers may also be elevated in chronic HS lesions, suggesting an IgE-related innate immune mechanism in HS pathogenesis.

3.3 | Involvement of other innate immune cells

In addition to the cell types mentioned above, HS is turning out to be a disorder of truly formidable complexity with several other cell types also potentially playing their part in HS disease. For example, CD56⁺ natural killer (NK) cell numbers may correlate inversely with...
time since initial HS disease presentation. NK cells are reported to co-localize with IL-32 expression in HS lesions, and lesional NK cells in patients with early HS show enhanced IFN-γ and granzyme B production capacity. Little is known of any role for Natural killer T cells (NKTs) invariant Natural killer T cells (iNKTs), γδ T cells and innate lymphoid cells (ILCs)—all innate immune cells of the lymphoid lineage and present at skin barrier surfaces.

Our understanding of the “fibroblast” in biomedicine, including dermatology, has recently undergone a seismic re-evaluation, and this heterogeneous family of cells are considered to be much more active in immune responses than thought previously. Given their known role in HS sinus tract formation and scarring, understanding how fibroblast-innate immune coordination functions in HS is likely to be a fruitful avenue for therapeutic exploration.

3.4 Pattern recognition receptors and inflammasomes in HS

There has been accumulating evidence for dysregulated pattern recognition receptors (PRR) signalling in HS. PRRs are germline-encoded host sensors that allow the innate immune system to detect broad classes of molecules that signal danger to the host. These molecules are defined in two classes: pathogen-associated molecular patterns (PAMPs) associated with microbial pathogens and damage-associated molecular patterns (DAMPs). Given the build-up of inflammatory material in HS (eg bacterial PAMPS like lipopolysaccharide (LPS) or DAMPs like DNA or ATP released from dying cells), it is intuitive that PRRs may propagate downstream inflammatory signalling. TLRs are the archetypal PRRs and the best studied of the five PRR superfamilies. Hunger et al have reported that TLR2 expression is elevated in HS lesions and was expressed on associated CD68+ macrophages and CD209+ DCs. TLR8 signalling is also upregulated in HS, along with several downstream signalling mediators. More recent transcriptomics studies in HS skin have further added to this picture, with TLR 3, 4 and 9 expression appearing to be elevated in HS and pathway analysis identifying the transcription factor NF-κB as a critical signalling hub. Interleukin-1 receptor-associated kinase 4 (IRAK4), another central signalling scaffold in many PRR and cytokine receptor pathways, may thus be a therapeutic target in HS. Indeed, several existing treatments for HS may directly or indirectly inhibit these signalling pathways. Still, there is conflicting evidence, with some studies suggesting reduced TLR expression, which may reflect a view that inflammation in HS results from a deficiency of antimicrobial immunity. While further studies are required to address the precise role(s) of TLR signalling in HS, current evidence supports a model of TLR overexpression and/or overactivation, although the precise receptor:ligand interactions remain unknown.

NOD-like receptors (NLRs) and their downstream inflammasomes are of interest in HS. These nucleotide-binding oligomerization domain (NOD)-like receptors act as intracellular sensors of both PAMPs (entering cells via phagocytosis or through pores), and of DAMPs (associated with cell stress). For example, NLRP3 and Caspase-1, which together with other inflammasome-forming components cleave IL-1β and IL-18, are overexpressed in HS, as well as in the related condition Pyoderma- associated suppurative hidradenitis (PASH). Given their importance in diseases like psoriasis and SLE is receptors from other PRR superfamilies that can sense RNA, DNA and C-type lectin receptors are understudied in HS. An exception is the finding of Orvain et al that overactive cytotoxic sensing of DNA, through the IFI16/STING pathway, may be responsible for aberrant keratinocyte function in HS (Figure 1B). This further illustrates that greater understanding of innate immune signalling will provide insights into HS pathogenesis. A summary of aberrant PRR expression studies in HS is provided in Table 2.

4 CHEMICAL INNATE IMMUNE BARRIER IN HS

4.1 Antimicrobial peptides and HS

Dysregulated expression of AMP in HS may impact homeostatic relationships between the skin barrier and the skin microbiome. Many inflammatory skin disorders display dysregulated AMP expression (eg defensins in psoriasis) and HS appears to be no exception. The direction of causality and functional outcomes, however, remains unclear. For instance, the expression of cathelicidin (LL-37) is induced in HS lesions, and it is thought to have differential effects at different disease stages: as an antimicrobial factor in early lesions, where it is thought to be neutrophil derived, and as an inducer of epithelial cell hyperplasia and Th1/Th17 responses in chronic lesions. This duality of function underscores the difficulty in interpreting events that are characteristic of truly early HS lesions, as well as the broader difficulty in interpreting whether AMP are the cause or result of inflammation and barrier breakdown in HS. This is also true of reported S100A8/9 expression as mentioned previously. While there are conflicting reports of altered expression levels for some AMP, defensins, in particular, others appear to have clear associated profiles. Reports of LCN2 expression correlating with neutrophilia and disease severity are one example, and another is the loss of dermcidin (DCD) expression in early HS, which may indicate impaired eccrine sweat gland function in diseased skin. AMP expression in HS is likely to be mediated in several ways, including via cytokine signalling (particularly IL-17, IL-22, IL-23 and IL-32), altered PRR signalling and functional inhibition by MMP2. The dysregulation of AMP points to an impairment of functional immune barriers in HS. Much work remains to be done to understand the causes of their presence/absence at different stages of HS, particularly with regards to microbiome changes, and what ramifications these have for disease pathology. A summary of some of the key AMP studied in HS and their expression is presented in Table 2.
4.2 Innate immune cytokines in HS

Cytokines have long been the major area of research in the HS field due to their vital role in inflammation. In the skin, keratinocytes and local innate immune cells secrete cytokines in response to stress triggers (PRR sensing, cell death, etc), which can then further activate the inflammatory response through vasodilation, immune cell recruitment and activation and cell toxicity. Many autoimmune and autoinflammatory conditions result from inappropriate cytokine responses, and biologic therapies targeting these chemical mediators have had an enormous impact on inflammatory skin disease over the last 20 years. The only approved biologic for HS, adalimumab, targets the key pro-inflammatory cytokine player in the innate immune response, TNF-α, although several other therapies targeting cytokines have also shown promise in open label studies. Many skin barrier cytokines such as IL-17, IL-22 and IL-12/23 have been implicated in HS and are the focus of active research. We limit our discussion here to cytokines that may be involved during the early stages of HS barrier disruption, namely TNF-α, IL-1 family cytokines, IL-10 and IFN-γ, which are summarized in Table 2. A current view of the cytokine interactions and cell types considered important in HS is presented in Figure 2, as well as some of the therapeutic

| Cytokine | Elevated expression | Reduced expression | No change |
|----------|---------------------|--------------------|-----------|
| IL-1α    | 128, 170, 171       |                    |           |
| IL-1β    | 53, 67, 69, 124, 125|                    |           |
| IL-18    |                     |                    |           |
| IL-36    | 73, 126, 127        |                    |           |
| IL-10    | 53, 99, 117, 135, 170| 56, 172            |           |
| TNF-α    | 67, 68, 77, 121, 125, 173| 99 | 32, 53, 170 |
| IFN-γ    | 53, 71, 73, 114, 170| 67, 135, 174       |           |
| Chemokines |                   |                    |           |
| IP-10    | 37, 53, 78         |                    |           |
| CCL5     | 53, 135            |                    |           |
| CCL20    | 53, 73, 135        |                    |           |
| Pattern recognition receptor | Elevated expression | Reduced expression | No change |
| TLR2     | 64                 | 99                 |           |
| TLR3     | 53                 | 99                 |           |
| TLR4     | 53, 71             | 99                 |           |
| TLR7     | 71                 | 99                 |           |
| TLR8     | 97                 |                    |           |
| TLR9     | 53                 | 99                 |           |
| NLRP3    | 55, 100            |                    |           |
| Pyrin    | 175                |                    |           |
| IFI16    | 37                 |                    |           |
| AMP      | Elevated expression | Reduced expression | No change |
| S100A7   | 20, 53, 55, 79, 83 |                    |           |
| S100A8   | 20, 53, 55, 83     |                    |           |
| S100A9   | 20, 53, 55, 83     |                    |           |
| β-defensin 2 | 20, 79, 97, 176, 177| 99 | 56 |
| β-defensin 3 | 178                |                    |           |
| Lipocalin | 52, 56, 84        |                    |           |
| Dermcidin | 97                 | 178                |           |
| Cathelicidin (LL-37) | 32, 33 |                    |           |
| Other soluble innate inflammatory mediators | Elevated expression | Reduced expression | No change |
| Complement C5a | 136-139 |                    |           |
| Leukotriene LTB4 | 144 |                    |           |
4.3 | TNF-α

Release of TNF-α by macrophages and NK cells is a hallmark of early signalling by the innate immune system and leads to the classic inflammatory responses of vasodilation and the subsequent influx of immune cells. While data on TNF-α expression in HS lesions and blood are mixed, the evident efficacy of adalimumab in HS treatment is a clear indicator that this cytokine plays at least some role in pathogenesis. Still, adalimumab is ineffective for a significant proportion of HS patients (41–58%), which may reflect the complex biology of TNF-α signalling through its two different receptors in the skin. TNF-α expression may not correlate with disease severity in HS, and a recent study by Marzano et al has revealed a “therapeutic window” in early HS disease when anti-TNF-α treatment may prevent progression. These data may indicate that this cytokine is in fact an early key domino in the dysregulated immune cascade of HS, and that early intervention to block its activity can prove effective.

4.4 | IL-1 family cytokines

The IL-1 family cytokines IL-1α and IL-1β are highly overexpressed in HS differentiating it from other dermatoses such as psoriasis and atopic dermatitis, unlike IL-22, IL-17 or IL-1RA which are dysregulated in all three diseases. They are critical cytokines in the early innate immune response and promote further pro-inflammatory cytokine secretion (including IL-17), integrin expression and vasodilation at the inflamed site. A recent study employing bulk and single-cell transcriptomics has identified IL-1 signalling as a key factor in HS. Secreted primarily by mononuclear phagocytes, members of the IL-1 family are dysregulated in HS, most notably the archetypal IL-1β. The latter cytokine is secreted by macrophages and keratinocytes in patient skin and is also elevated in HS serum. In addition, IL-18 is elevated in lesional HS skin, and together with IL-1β requires post-translational cleavage by caspase-1; potentially an evolved mechanism to tightly control the expression of these potent IL-1 family members. Although IL-1β (released by macrophages in response to phagocytosed debris from occluded HF) appears to be a key trigger of inflammation in HS and is an attractive HS hypothesis, further supportive evidence is needed.

**FIGURE 2** Critical innate immune cytokine networks in HS. Here, we illustrate some of the cytokine networks currently considered to be important in HS pathogenesis and some of the drugs being used to target these pathways in the clinic. Purple boxes indicate drugs reported to have been used in HS in case reports or clinical trials. Keratinocytes from the epithelium or HF release elevated levels of several inflammatory molecules activate innate immune cells via their cytokine receptors and PRRs. The initial triggers for keratinocyte stress remain unknown. Activated macrophages then release cytokines, which shape the subsequent innate and adaptive response. IL-1 cytokines, IL-23 and IL-17 are major targets of therapeutic intervention, as are its upstream mediators/cells. Figure created using BioRender.com.
Other IL-1 family cytokines are reported to be elevated in HS lesions, including all three IL-36 isoforms, which may trigger inflammation via DC activation and promotion of keratinocyte hyper-proliferation.\textsuperscript{126} Counterintuitively, the immunosuppressive IL-1 family cytokines IL-37 and IL-38 are elevated in perilesional tissue, although this may indicate a possible imbalance between agonistic and antagonistic interleukins in adjacent HS skin sites, as has been reported in psoriasis.\textsuperscript{126,127} Several small studies trialling IL-1α and IL-1β biologic therapies suggest that these cytokines are important therapeutically.\textsuperscript{128-130} A Phase II trial on the anti-IL-1α biologic bemekimab, conducted by Gottlieb et al, is encouraging including for those patients unresponsive to anti-TNF-α therapy.\textsuperscript{120}

4.5 | IL-10

IL-10 is the archetypal anti-inflammatory or immunosuppressive cytokine,\textsuperscript{131} and it is rather curious that this cytokine is elevated in inflammatory lesions and serum of HS patients.\textsuperscript{57} As with IL-1α and IL-1β, elevated levels of IL-10 differentiates HS from other dermatoses. Signalling through its widely expressed cognate receptor, IL-10 can suppress pro-inflammatory signalling and T-cell activation through NF-κB inhibition and other mechanisms.\textsuperscript{52} It is also a critical modulator of immune homeostasis at other barrier sites, such as the gut, particularly via its effect on macrophage function; loss of IL-10 leads to very severe inflammation.\textsuperscript{133} Its elevation in HS may reflect an influx of immunosuppressive regulatory T cells during disease progression, recruited to quell inflammation. Thus, it is possible that it is a compensatory reaction to excessive macrophage activation in earlier disease. Moreover, increased IL-10 may inhibit Th22 cells, which are critical in maintaining the expression of downstream effectors of barrier function such as AMPs.\textsuperscript{1,117} As the elevation of IL-10 levels is uncommon in other inflammatory dermatoses, this aspect of HS biology warrants particular investigation, not least to pinpoint its cellular source and to identify likely target cells and associated signalling pathways.

4.6 | IFN-γ

Despite earlier conflicting data, IFN-γ does appear to be an important factor in the initiation of HS.\textsuperscript{53,67,114,117,118} Several indirect observations suggest IFN-γ-induced events feature in HS lesions: Th1/17 cell responses, activated macrophages and IFN-γ-stimulated gene expression (ISGs) are all induced strongly.\textsuperscript{34,37,55} Indeed, there are several reports of elevated IFN-γ levels in varying cell types in both HS lesions and blood (eg keratinocytes and NK cells), further supported by more recent transcriptomic analysis.\textsuperscript{53,71,73} The literature also contains studies that report no significant difference in IFN-γ expression between HS lesional and control skin, and some even reporting significant decreases in IFN-γ levels in HS serum.\textsuperscript{53,57} At least part of this discrepancy may be explained by differences in methodological approaches taken to measure levels of this critical cytokine.\textsuperscript{57} Still, IFN-γ does seem likely to be a driver of HS pathogenesis, given its capacity to activate several of the key cell types involved. Further insights into the potential importance of IFN-γ in HS may be gleaned from our understanding of how IFN-γ mediates “collapse” of the immune privilege that is characteristic of the cycling portion of healthy growing (anagen) HF in inflammatory HF disorders.\textsuperscript{26,40,41}

4.7 | IP-10 and chemokines

The recruitment of immune cells via a chemokine gradient is a critical feature of functioning immune responses, and this recruitment is dysregulated in a variety of inflammatory diseases, including dermatoses like atopic dermatitis.\textsuperscript{134} Several chemokines appear altered in HS tissue.\textsuperscript{57} For example, interferon gamma-induced protein 10 (IP-10, also known as CXCL10) is consistently elevated in HS, where lesional keratinocytes produce elevated levels of this chemokine in response to various PRR ligands.\textsuperscript{37,53,78} IP-10 is also important for recruitment of monocytes, macrophages DCs and T cells.\textsuperscript{54} and this chemokine further influences B-cell biology; an immune cell type receiving increasing attention in HS pathobiology.\textsuperscript{78,81}

Hotz et al have shown that the chemokines CCL5 and CCL20 are more highly expressed at an RNA level by keratinocytes in HS tissue and that CCL5, like IP-10, shows similar elevations in secretion upon PRR stimulation.\textsuperscript{53,135} While several other chemokines have been investigated in HS, our understanding of the specific pathways involved and their associated dynamics for immune cell recruitment in HS requires significant further study.\textsuperscript{57,61}

5 | OTHER SOLUBLE INNATE IMMUNE MEDIATORS IN HS

5.1 | The complement system

As previously alluded to, HS is exceptional in its high degree of engagement with a multiplicity of immune system actors. Therefore, it is perhaps not surprising that a putative role for the complement system is also a feature of the rapidly developing landscape of HS. While most complement proteins are synthesized in the liver, they can also be produced locally, including by several cell types implicated in HS pathogenesis (eg mast cells, macrophages, keratinocytes and fibroblast).\textsuperscript{34} Several studies have implicated each of the three complement system pathways in HS pathogenesis, although it remains unclear whether these purported associations are causal.\textsuperscript{136,137} Key complement proteins elevated in HS lesions and blood include C5a and C5b-9, although a broader proteomics approach has revealed a more global dysregulation of the complement system.\textsuperscript{138,139} Moreover, given that C3 levels are reduced in psoriasis after anti-TNF therapy, it is possible that some reciprocally related pathways may also be active in HS.\textsuperscript{137,140} In addition, the complement system may be active in the formation of the HS inflammasome, for
example via complement activation of the P2X7 receptor. It is also plausible that the complement cascade in HS disease is triggered by microbial factors. There remains some potential that the complement pathway may be exploited as a therapeutic target, although the recent SHINE study, targeting C5a via the monoclonal antibody IFX-1, found no benefit compared to placebo.

5.2 | Secreted lipid mediators

Lipids and fatty acids are an important part of the skin homeostasis and are among the earliest identified modulators of immune cell function. Investigations on the status of immunomodulatory polyunsaturated fatty acids (PUFA) and their associated biosynthetic pathways has been conducted in HS lesions by combining targeted lipidomics and transcriptomics approaches. A latter approach found dysregulation of lipid-mediated pathways in HS, including those involving skin-infiltrating macrophages. In particular, metabolites of the 5-lipoxygenase (5-LO) pathway were elevated in HS, including the inflammatory leukotriene LT4B4, while the anti-inflammatory 15-LO pathway was downregulated. By contrast, some inflammatory mediators of the cyclooxygenase pathway, mediated by COX1 and -2 enzymes, were reduced in HS.

6 | EFFECTS OF HS-ASSOCIATED GENETIC MUTATIONS ON INNATE IMMUNE FUNCTION

While the genetics of HS have been extensively reviewed elsewhere, we briefly mention here how some genetic associations are linked with a dysregulated innate immune response in HS. Several mutations have been discovered in particular HS cohorts, including in genes that encode the γ-secretase protein complex, including NCSTN, PSENEN and PSEN1. This secretase is critical for Notch signalling. This pathway also interacts with many developmental and homeostatic processes, including haematopoiesis, APC-T cell interactions, IL-10R processing and in the regulation of IL-10 secretion. Additional genetic mutations discovered in HS are directly involved in innate immunity, such as mutations in MYD88 (encoding an essential TLR signalling adaptor), in DEFB103 and DEFB4 AMP genes, and in TNF-α and IL-12 receptor genes. Readers are advised to interpret the impact of these mutations cautiously, as it is not yet clear how these may impact on immune dysregulation. These studies often lack statistical power, and so future multi-omics data should help clarify the relevance of these and other genotype-phenotype associations in HS.

7 | THE SKIN MICROBIOME “BARRIER” IN HS

Microbiome research focused on health and disease has advanced significantly in recent years and the study of the cutaneous microbiome in HS is no exception. The normal skin microbiome has adapted to a relatively nutrient poor and acidic environment and is a crucial part of the skin’s outermost barrier, preventing infection through competition and antimicrobial mechanisms. Despite the frequent use of antimicrobial therapy in HS, little was known about patient skin and gut microbiomes until quite recently. Recent studies regarding the HS skin and gut microbiomes have been extensively reviewed elsewhere, but there are a few key considerations which we will reflect on here for future research.

Several reports have demonstrated alterations in microbial community structure and diversity in HS, with studies suggesting that Prevotella and Porphyromonas species may dominate the cutaneous microbiome of HS lesions, with a concomitant reduction in the prevalence of the commensal Staphylococcus epidermidis. A recent study of the microbiome of “clinically normal” skin in HS patients has also revealed alterations in microbial structure that is reminiscent of lesional sites. This observation, along with the suggestion that IL-17 immunity becomes dysregulated in HS, may indicate that subclinical HS skin may have a microbiome that predisposes it to HS pathology. New studies are needed to define the host: microbe relationships that govern alterations in microbiome structure and gene expression, and to define the functional consequences of a dysbiosis. Biofilm formation in sinus tracts and HF of chronic HS lesions is one such consequence, but the events that lead to this outcome are still unclear.

It has long been appreciated that human HF are sites of active microbial colonization, distinct from that in the epidermis where these microbiomes regulate host immune mechanisms via microbe-immune cells crosstalk that can influence homeostasis and inflammation. Alterations in follicular microbiome, including dysbiosis, have been described in some inflammatory cutaneous diseases, including those involving the HF like folliculitis, acne vulgaris, alopecia areata and cicatricial or scarring alopecias. This may be particularly relevant in the upper, immunocompetent region of the HF, a site rich in Langerhans cells. Moreover, how such dysbiosis in the upper HF may affect the usually “immune privileged” proximal HF is of particular interest. So far the main bacterial constituents of the HF microbiome include Cutibacteria, Corynebacteria, Staphylococci and Streptococci, several of which are notable in HS studies. We need much more insight into the nature of the HF host: microbe interface in HS (e.g., resident immune cells, AMP expression). Another important aspect for consideration in future studies is the link between dysbiotic microbiomes and the several HS comorbidities, such as obesity, inflammatory bowel diseases (IBD) and metabolic diseases like type 2 diabetes. Furthermore, the gut-skin axis and in particular the link between the gut microbiome (and its metabolic output) and inflammatory cutaneous diseases like HS is becoming increasingly apparent, and warrants study in the context of HS.
For instance, reduced short chain fatty acid (SCFA) output from the gut microbiome has long been linked with IBD and associated inflammation, and can be directly mapped to immunological effects on T-cell polarization and macrophage function.164-166

Aside from bacteria, other microorganisms which form part of the skin microbiome have also been linked with complications in HS. For example, the disrupted microbiome in IBD and HS may involve yeast outgrowth, although this may be a side effect of immunomodulatory therapy.167 Future studies will be required to interrogate alteration to the HS skin and gut mycobiome and virome. Many of the HS microbiome studies to date suffer from limited statistical power, and so care must be taken when drawing causal or correlative associations between the disease and known risk factors.158 Thus, in order to obtain a more comprehensive view of how an altered microbiome impacts on HF disease we will need studies with much larger HS cohorts, to remove the effect of confounding variables such as patient body mass index (BMI), smoking status and use of antimicrobial therapies.168 In addition, in order to establish the functional consequences of microbial community alteration (e.g. bacterial metabolite profiles, secreted immunomodulatory products) additional metagenomics and meta-transcriptomics will be needed in conjunction with metabolic profiling.

8 | CONCLUSIONS AND PERSPECTIVES

Despite the remarkable and often dizzying flurry of recent research activity into the extraordinarily complex pathogenesis of HS, there remain significant and fundamental gaps in our knowledge. We need now to much more carefully dissect how these and other immune and stromal components drive the distinct phases of HS disease, principally its initiation. Thus, this is likely to require a much more sophisticated analysis of the role of the HF and pilosebaceous unit. Reflecting on the wealth of already published data, we consider that there is a convincing case that HS is initiated by alterations in barrier immunity, not least the haired-skin barrier in intertriginous and sexual body sites. While the exact causal relationships of barrier defects in HS are not yet clear, they provide numerous promising therapeutic targets. This progress has been exemplified by the relative success of adalimumab therapy, as well as the promise of ongoing studies targeting other innate immune mediators. Intervening early in HS will not only require strategies to limit or blunt the emerging inflammation, but also to support barrier homeostasis and repair.169

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

DGWJ performed the literature search and wrote the first draft of the review. DJT and BK co-wrote and revised the manuscript.

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